THE JOURNAL OF GENERAL CHEMISTRY OF THE U.S.S.R.

(ZHURNAL OBSHCHEI KHIMY)

Volume 26, No. 10

October, 1956

(A Publication of the Academy of Sciences of the U.S.S.R.)

IN ENGLISH TRANSLATION

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CONSULTANTS BUREAU, INC.
227 West 17th Street
New York 11, N.Y.

Printed in the United States

Annual Subscription	$175.00
Single issue	30.00

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SIGNIFICANCE OF ABBREVIATIONS MOST FREQUENTLY ENCOUNTERED IN SOVIET PERIODICALS

FIAN	Phys. Inst. Acad. Sci. USSR.
GDI	Water Power Inst.
GITI	State Sci.-Tech. Press
GITTL	State Tech. and Theor. Lit. Press
GONTI	State United Sci.-Tech. Press
Gosenergoizdat	State Power Press
Goskhimizdat	State Chem. Press
GOST	All-Union State Standard
GTTI	State Tech. and Theor. Lit. Press
IL	Foreign Lit. Press
ISN (Izd. Sov. Nauk)	Soviet Science Press
Izd. AN SSSR	Acad. Sci. USSR Press
Izd. MGU	Moscow State Univ. Press
LEIIZhT	Leningrad Power Inst. of Railroad Engineering
LET	Leningrad Elec. Engr. School
LETI	Leningrad Electrotechnical Inst.
LETIIZhT	Leningrad Electrical Engineering Research Inst. of Railroad Engr.
Mashgiz	State Sci.-Tech. Press for Machine Construction Lit.
MEP	Ministry of Electrical Industry
MES	Ministry of Electrical Power Plants
MESEP	Ministry of Electrical Power Plants and the Electrical Industry
MGU	Moscow State Univ.
MKhTI	Moscow Inst. Chem. Tech.
MOPI	Moscow Regional Pedagogical Inst.
MSP	Ministry of Industrial Construction
NII ZVUKSZAPIOI	Scientific Research Inst. of Sound Recording
NIKFI	Sci. Inst. of Modern Motion Picture Photography
ONTI	United Sci.-Tech. Press
OTI	Division of Technical Information
OTN	Div. Tech. Sci.
Stroiizdat	Construction Press
TOE	Association of Power Engineers
TsKTI	Central Research Inst. for Boilers and Turbines
TsNIEL	Central Scientific Research Elec. Engr. Lab.
TsNIEL-MES	Central Scientific Research Elec. Engr. Lab. – Ministry of Electric Power Plants
TsVTI	Central Office of Economic Information
UF	Ural Branch
VIESKh	All-Union Inst. of Rural Elec. Power Stations
VNIIM	All-Union Scientific Research Inst. of Meteorology
VNIIZhDT	All-Union Scientific Research Inst. of Railroad Engineering
VTI	All-Union Thermotech. Inst.
VZEI	All-Union Power Correspondence Inst.

Note: Abbreviations not on this list and not explained in the translation have been transliterated, no further information about their significance being available to us. – Publisher.

THE PREPARATION OF SODIUM PHOSPHOTUNGSTATES FROM TUNGSTIC ACID AND SODIUM PHOSPHATES

E. A. Nikitina and E. V. Buris

According to the literature [1], sodium phosphotungstate may be obtained by the reaction between disodium hydrogen phosphate and tungstic acid. The conditions for carrying out the reaction have not, however, been studied.

EXPERIMENTAL

I. The reaction $Na_2HPO_4 + 12H_2WO_4 \rightleftharpoons Na_2H_5[P(W_2O_7)_6] + 10H_2O$ is reversible, and our aim was to examine the conditions under which it could be moved further to the right.

The tests carried out confirmed that the formation of the heteropolyanion $[P(W_2O_7)_6]^{VII}$ takes place only with the white form of tungstic acid, obtained at room temperature, as has been shown earlier by E. A. Nikitina and O. N. Sokolova [2]; yellow tungstic acid, precipitated at higher temperature, is practically incapable of forming complexes with the phosphoric acid residue.

Temperature is an important factor in bringing about formation of the complex. It has been established experimentally that the optimum temperature is 50°. At 60-80° the reverse reaction, i.e. decomposition of the heteropolyanion, predominates, and precipitation of tungstic acid in the unreactive form is observed.

The yield of phosphotungstate increases considerably if a 2 – 3-fold excess of tungstic acid is used; further increase in the amount of H_2WO_4 in excess of that required by the reaction equation has no effect, since the yield is not increased further.

In its final form the preparation of disodium phosphotungstate was carried out as follows: 200 g of sodium tungstate was dissolved in 1 liter of water, the solution was filtered, and white tungstic acid precipitated from it by the addition of 100 ml of concentrated nitric acid (tested for complete precipitation). Before precipitating the H_2WO_4 the sodium tungstate solution had to be cooled to approximately 15° (this was necessary to prevent undesired heating of the solution during the addition of the nitric acid and the consequent formation of the less reactive yellow form of H_2WO_4).

The tungstic acid obtained was washed carefully by decantation with warm water. Washing was continued until the washings were free from NO_3' ion (tested with diphenylamine and sulphuric acid). The amount of water used was approximately 3 liters. The washing of the precipitate was carried out as quickly as possible, so that the time taken did not exceed 24 hours. The washed tungstic acid, which should appear as a pale yellow curdy mass, was carefully pressed out and used immediately for the synthesis. The yield of the pressed tungstic acid was 94%, its water content approximately 80%.

500 g of tungstic acid containing approximately 20% of the monohydrate was placed in a round-bottomed heat-resistant glass flask of 2 liters capacity; 7 g of $Na_2HPO_4 \cdot 12H_2O$ was then added, followed by 1.3 liters of distilled water. The reaction mixture was heated with uninterrupted mechanical stirring up to 50° over a period of 3 hours and afterwards left to stand for 15-20 hours. The formation of sodium phosphotungstate was considered complete when a sample of the solution, filtered from excess tungstic acid, gave no precipitate of H_2WO_4 on addition of a few drops of hydrochloric acid (d 1.12). The sodium phosphotungstate solution obtained was filtered from the excess unused tungstic acid. In cases where colloidal tungstic acid passed through the filter, a thin layer (0.5 cm) of washed tungstic acid was placed on it and filtration carried out through the H_2WO_4 layer.

The transparent sodium phosphotungstate solution obtained (d 1.02-1.03, volume approximately 1 liter) was evaporated on a water bath until crystals of the salt appeared. Evaporation may also be carried out on a burner with asbestos gauze, by gently boiling the solution until a crystalline salt layer appears on the surface. After evaporation the solution was cooled to room temperature, the precipitated salt crystals filtered off, the filtrates from the crystal separation collected from several batches and again evaporated. The salt crystals were dried in air for 1.5-2 hours or in a drying oven at 50° for 1/2 hour. The yield of salt in the first fraction was 60%; on treatment of the filtrates the yield was raised to 80-90%.

The analyses of salt samples carried out are given in the table and show that the composition of the salt varies between those of the di- and trisubstituted salts (Specimens I-III).

Analyses* of Sodium Phosphotungstates

	Content (%)		
	P_2O_5	Na_2O	WO_3
Calculated			
For the disubstituted salt	2.43	2.19	95.44
For the trisubstituted salt	2.41	3.15	94.44
For the tetrasubstituted salt	2.38	4.16	93.45
Found			
Specimen I	2.47	3.14	94.39
Specimen II 60	2.49	2.22	94.71
Specimen III	2.46	2.25	95.28
Specimen IV	2.42	4.12	93.45
Specimen V	2.39	3.55	94.06

* The analyses were carried out as described earlier [3], and consisted of the determination of H_2O, P_2O_5 and Na_2O. The tungstic anhydride was obtained by difference.

II. The reaction between tungstic acid and trisodium phosphate was also carried out to obtain sodium phosphotungstate. The preparation conditions for the starting materials were analogous to those of the previous experiment. The tungstic acid was used in 200% excess of the theoretical amount, the trisodium phosphate in the theoretical amount, according to the equation $12H_2WO_4 + Na_3PO_4 \rightleftharpoons Na_3H_4[P(W_2O_7)_6] + 10H_2O$.

Sodium phosphotungstate was obtained in 60% yield from the first fraction; its composition varied between those of the tri- and tetrasubstituted salts. The analyses results of samples obtained from trisodium phosphate are also given in the table (Specimens IV and V). All the phosphotungstate specimens obtained were free from SO_4'', Cl', heavy metal and MoO_4'' impurities, and exceeded the purity requirements demanded for chemically pure specimens.

The advantage of the method described is that the prepared specimens do not require to be recrystallized. The salt solutions obtained are free from any turbidity arising by partial hydrolysis of the salt.

SUMMARY

1. A method for preparing sodium phosphotungstates from tungstic acid and di- and trisubstituted sodium phosphates has been worked out.

2. The yield of the salts, without using the filtrates from the first fraction, is 60%.

3. The phosphotungstates obtained are of varied composition. Phosphotungstates with compositions between those of the di- and trisubstituted salts are obtained from disodium hydrogen phosphate; phosphotungstates with compositions between those of the tri- and tetrasubstituted salts are obtained from trisodium phosphate.

LITERATURE CITED

[1] Abegg. Handb. anorg. Chem. 4, 989 (1921).

[2] E. A. Nikitina and O. N. Sokolova, J. Gen. Chem. 23, 1437 (1953) (T.p. 1505).*

[3] A. V. Rakovsky and E. A. Nikitina, J. Gen. Chem. 1, 243 (1931).

Received October 26, 1955

Chemical Reagent Institute

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* T. p. = C. B. Translation pagination.

A STUDY OF THE REDOX PROPERTIES OF GERMANIUM HETEROPOLYACIDS

Z. F. Shakhova and R. K. Motorkina

The heteropolyacids of molybdenum and tungsten are fairly powerful oxidizing agents. A whole series of methods of determining different elements (silicon, germanium, phosphorus, arsenic, etc.) is based on the ability of heteropolyacids of these elements to be reduced to heteropoly "blues." In all such cases the conditions of formation are chosen so that only the heteropolycompounds are reduced while excess molybdate or tungstate remains unreduced.

The authors of the proposed methods, without making a special study of the question, assert that molybdenum or tungsten combined in a heteropolycomplex are reduced more readily than in the uncombined state, i.e. have higher redox potentials.

1. Working Method and Preparation of Solutions

The redox potentials of different heteropolyacids of germanium were determined by the method given for the determination of the redox potential of tungsten [1]. The total amount of molybdenum or tungsten in the original heteropolycompounds was determined by potentiometric titration with a 0.1 N solution of chromous sulfate, after which a quantity of chromous solution equal to half that used in the titration was added to another equal portion of the solution and the potential of the system obtained was measured. The value of this potential is approximately equal to E_0, since under these conditions the concentration of oxidized form in the formula $E = E_0 + \frac{RT}{nF} \ln \frac{[ox]}{[red]}$ is equal to the concentration of the reduced form and $E = E_0$. Divalent chromium was chosen as oxidant since this makes it possible to titrate both molybdenum and tungsten in similar conditions, i.e. by using divalent chromium a comparative picture may be obtained of the redox properties of the heteropolycompounds of both molybdenum and tungsten.

The measurements were made using a P4 potentiometer. A platinum electrode was used as indicating electrode, a saturated calomel electrode as reference electrode. Titration and potential measurement were carried out in a current of carbon dioxide in a beaker of 50 ml capacity fitted with a stopper having openings for a stirrer, the platinum electrode, a salt bridge filled with saturated KCl solution, and tubes for entry and exit of the carbon dioxide. The chromous sulfate was prepared by the method given by A. I. Busev [2], but the quantity of sulfuric acid in the solution was increased threefold, since reduction of the chromium is not complete in three weeks at the H_2SO_4 concentration recommended by the author. The chromous solution was standardized potentiometrically under the following conditions with a standard solution of potassium dichromate prepared by dissolving 1.1608 g of dried salt in 250 ml of water (0.09465 N solution): 5 ml 4 N sulfuric acid and 10 ml water were added to 5 ml potassium dichromate solution, the solution was saturated with carbon dioxide for 20-30 minutes and titrated with divalent chromium in a current of carbon dioxide. One titration curve is given in Figure 1.

2. Titration of Ammonium Molybdate Solution

Before proceeding to a determination of the redox potentials of molybdenum heteropolyacids, we determined the redox potentials of systems in which the molybdenum is not bound in a complex. A solution of 2.03 g of chemically pure ammonium paramolybdate in 100 ml water was used as the starting solution. The MoO_3 content in the solution was determined by precipitation with hydroxyquinoline according to Berg [3]. The solution contained 16.59 mg MoO_3 in 1 ml. The titration was carried out by the method recommended for the quantitative determination of molybdenum [4]: 12.5 ml concentrated hydrochloric acid and 12.5 ml water were added to 2 ml ammonium molybdate solution, the solution was warmed to 90° and titrated with $CrSO_4$ solution in a current of carbon dioxide at 90°.

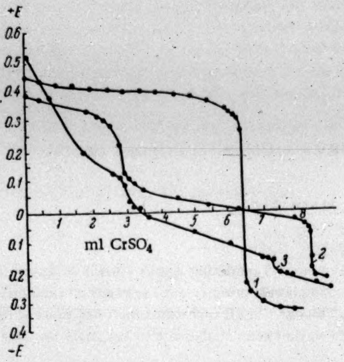

Fig. 1. Titration of $K_2Cr_2O_7$ with $CrSO_4$ solution (Curve 1) and titration of Mo^{VI} with $CrSO_4$ solution (Curve 2 – in ammonium molybdate, Curve 3 – in germanomolybdic acid).

TABLE 1

Volume of $CrSO_4$ solution (in ml)	E_0 (relative to the hydrogen electrode,* in V)	
	at 90°	at 22°
1.59	+0.648 +0.654 +0.656	+0.622 +0.622 +0.630
6.36	+0.258 +0.263 +0.266	+0.243 +0.258 +0.253

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* The measurements were carried out using a calomel electrode which remained at a constant temperature (22°); the potential of the calomel electrode relative to the hydrogen electrode is 0.248 V.

In the molybdenum titration the initially colorless solution became pale green, then brown and finally green without passing through blue. The titration curve is given in Figure 1 (Curve 2).

The molybdate titration curves with divalent chromium have two inflections, corresponding to the potential jumps on the change from Mo(VI) to Mo(V) and from Mo(V) to Mo (III):

For the determination of the redox potentials of the Mo^{VI}/Mo^{V} and Mo^{V}/Mo^{III} systems, 12.5 ml water, 12.5 ml concentrated hydrochloric acid, and first 3.18/2 = 1.59 ml and secondly a further 6.36 + 3.18/2 = 4.77 ml of $CrSO_4$ solution (the total amount of solution in the second case was 6.36 ml) were added to 2 ml ammonium molybdate solution, and the potentials measured. The results obtained are given in Table 1.

The mean value of E_0 for the system Mo^{VI}/Mo^{V} at 90° is +0.651 V, at 22° +0.623 V.

3. Titration of Germano Molybdic Heteropolyacid Acid Solution

The titration of germanomolybdic acid was carried out under the same conditions as the molybdate titration. The titration curve is given in Figure 1 (Curve 3).

In this case, as in the molybdate titration, no "blue" formation took place. The heteropolycompound is evidently broken down, since $GeCl_4$ is evolved on warming with hydrochloric acid.

In the germanomolybdic acid titration at 22° the potential of the system changes suddenly at the beginning of the titration; on adding the first portion of $CrSO_4$ solution molybdenum blue appears. On further addition of the reductant the molybdenum is reduced, while the heteropolycompound is evidently broken down as soon as the blue color of the solution disappears. When the amount of hydrochloric acid added for the titration is reduced, the potential jumps become less pronounced.

The results obtained in the determination of the redox potentials of germanomolybdic acid by the method described above are given in Table 2.

It can be seen from the results obtained that the potentials measured are considerably lower than the potentials of molybdenum which is not bound in a complex (0.623 V; see Table 1). This method of determining redox potentials is evidently inapplicable to molybdenum heteropolyacids. The heteropolyanion apparently remains intact only so long as reduction does not proceed beyond the stage of blue formation, i.e. when only a part of the molybdenum is reduced to the pentavalent state, all the remaining molybdenum is hexavalent, but on further reduction of the molybdenum the heteropolyanion is broken down. Since the formation of the blue color is also a qualitative characteristic of the heteropolyanion reduction, it was decided to determine the potential of the germanomolybdic acid – germanomolybdenum blue system.

TABLE 2

Volume of $CrSO_4$ solution (in ml)	E_0 (relative to the hydrogen electrode, in V) at 90°	E_0 (relative to the hydrogen electrode, in V) at 22°
1.68	–	+0.547
	+0.634	+0.551
	+0.647	+0.553
6.70	+0.250	+0.160
	+0.254	+0.157
	–	+0.161

TABLE 3

System	E_0 (relative to the hydrogen electrode, in V)
Mo^{VI}/Mo^{V}	+0.536
	+0.534
Mo^{V}/Mo^{III}	+0.240
	+0.229
	+0.229

Synthesis of the germanomolybdenum blue was carried out by the following method: 50 ml of 5% Mohr's salt (ferrous ammonium sulfate), 30-40 ml of ethyl ether and 18-20 ml of 1:1 sulphuric acid in portions of 5-6 ml were added to a separating funnel containing 10 ml of germanomolybdic acid solution synthesized by the ether method and containing 1.0 mg GeO_2 in 1 ml. The blue was extracted with ether for 1-2 minutes, the ether layer separated and the aqueous layer containing excess reductant rejected. The ether extract was again placed in the separating funnel, 50 ml of water was added and extraction renewed for 1-2 minutes without acidification. The ether layer was decolorized and the blue passed into the aqueous layer which was diluted to 100 ml and used as the original solution for the measurements.

Determination of the $Mo^{V}:(Mo^{VI} + Mo^{V})$ ratio was carried out by the following method: first, the germanomolybdenum blue solution was titrated with potassium dichromate solution to the potential jump and a slight excess of dichromate added; the solution obtained was then titrated with standard $CrSO_4$ solution, with which three potential jumps were observed: the first on reducing the excess dichromate, the second after reduction of all the Mo^{VI} to Mo^{V} and the third when all the molybdenum had been reduced to Mo^{III}. The titration with $CrSO_4$ solution gave the total amount of molybdenum in the blue while the preliminary titration with potassium dichromate gave the amount of molybdenum reduced to the pentavalent state, and the ratio $Mo^{V}:(Mo^{VI}+Mo^{V})$ in the blue was calculated. Afterwards the potential of germanomolybdic acid, to which had been added an amount of $CrSO_4$ equal to half that required for complete formation of the blue in the quantity of germanomolybdic acid taken, was measured. The potential obtained is then the redox potential of the germanomolybdic acid – germanomolybdenum blue system.

The results of the determination of pentavalent and of total molybdenum in 20 ml of germanomolybdenum blue are given in Table 4.

TABLE 4

Mo^{V} found (millimoles)	Total Mo content (millimoles)	Ratio $Mo^{V}:(Mo^{VI} + Mo^{V})$
0.068	0.270	1:4
0.071	0.270	1:3.8
0.068	0.272	1:4
0.077	0.271	1:3.5

TABLE 5

Total H_2SO_4 concentration (N)	E_0 (relative to the hydrogen electrode, in V) Series I	E_0 (relative to the hydrogen electrode, in V) Series II
0.0	+0.558	+0.548
0.2	+0.595	+0.605
0.5	+0.593	–
1.0	+0.600	+0.637
2.0	+0.611	–
5.0	+0.636	+0.676
10.0	+0.703	–
20.0	+0.801	+0.748
35.0	+0.786	–

TABLE 6

Series	E_0 (relative to the hydrogen electrode, in V)
I	+0.038
	+0.025
	+0.024
	+0.027
II	+0.062
	+0.052
	+0.052
	+0.045

The following conclusions may be reached from the results obtained: 1) on reduction of germanomolybdic acid, not all of the molybdenum in the complex is reduced, but only ~ 1/4 of it; 2) the reduced molybdenum is pentavalent and not lower, since Mo^{IV} and Mo^{III} can only be formed after all the molybdenum is reduced to the pentavalent state; 3) the heteropolycomplex apparently exists only so long as the blue exists and breaks down on further reduction.

To determine the redox potential of the germanomolybdic acid – germanomolybdenum blue system, 0.42 ml of $CrSO_4$ solution (the amount necessary to form the blue in half of the heteropolyacid taken) and varying amounts of 1 : 1 sulfuric acid were added to 2 ml of the original germanomolybdic acid solution and the potential of the systems obtained was measured (first series of tests).

To check the results obtained, the potentials of systems formed by mixing equimolecular amounts of germanomolybdic acid and the synthesized germanomolybdenum blue in the presence of varying amounts of sulfuric acid (without addition of $CrSO_4$) were measured (second series of tests).

All the results are given in Table 5.

From the data in Table 5 it is seen that the potential of the germanomolybdic acid – blue system with mineral acid present in the solution considerably exceeds the potential of the Mo^{VI}/Mo^{V} system for molybdenum not bound in a complex; the difference in the potential values is greater the higher the concentration of mineral acid. This conclusion agrees with experimental data from the use of heteropoly "blues" in analysis.

4. Titration of Sodium Tungstate Solution

The redox potentials of the W^{VI}/W^{V} system from sodium paratungstate and normal sodium tungstate were measured. The tungsten titration was carried out by the method proposed for the potentiometric determination of tungsten [5]: measured amounts of sodium paratungstate or tungstate in 5 ml solution were poured into 25 ml of concentrated hydrochloric acid and the solution titrated potentiometrically with standard $CrSO_4$ solution. The tungsten content in the tungstate solution was previously determined as WO_3 according to [6]. A distinct potential jump was obtained with quantities of WO_3 greater than 50 mg; a solution containing 15.66 mg WO_3 in 1 ml was therefore used for the redox potential determination, and 5 ml of this solution (78.30 mg WO_3) was taken for each titration. The titration curve is given in Figure 2 (Curve 1).

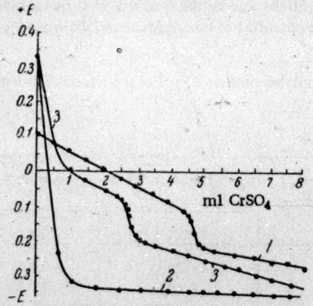

Fig. 2. W^{VI} titration curves with $CrSO_4$ solution. 1) In sodium tungstate, 2) in undecomposed germanotungstic acid, 3) in germanotungstic acid decomposed by warming with alkali.

For the determination of E_0, 2.33 ml of $CrSO_4$ solution was added to a mixture of 25 ml of concentrated hydrochloric acid and 5 ml sodium tungstate solution and the potential of the system measured after a definite time interval. E_0 became steady in 15 minutes and gave a mean value of +0.206 V. All measurements were made at room temperature (22°) without thermostat.

5. Titration of Germanotungstate Heteropolyacid Solution

In the titration of germanotungstic acid with $CrSO_4$ solution, the potential falls very rapidly with the first drops of $CrSO_4$, tungsten blue is formed, and no potential jump is observed at the equivalence point (Curve 2, Figure 2).

It is apparent that as a result of the stability of the hexavalent tungsten heteropolycomplex and the somewhat lower stability of the partly reduced complex, a definite concentration of W^{V}, much higher than the concentration of W^{VI} present in the solution as a result of the heteropolyanion dissociation, is formed in the titration by the very first drops of $CrSO_4$, the ratio $[W^{VI}]:[W^{V}]$ is almost zero, and the actual potential measured is that of the system Cr^{II}/Cr^{III}. In subsequent work, therefore, before determining the total amount of tungsten in an aliquot part of the germanotungstic acid, the complex was broken down by warming with alkali, while the redox potential was measured in the undecomposed heteropolyacid.

The titration curve is given in Figure 2 (Curve 3). The first part of the curve resembles the titration curve of the undecomposed heteropolyacid. A small amount of the latter is evidently reformed on acidifying the solution. The total amount of tungsten may be determined in this case; the potential jump is sufficiently distinct, although its absolute value is less than in the absence of germanium.

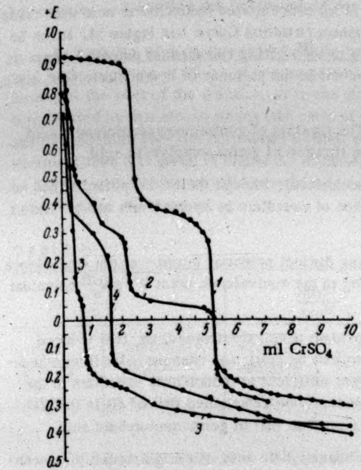

Fig. 3. Titration of NH_4VO_3 with $CrSO_4$ solution (Curve 1) and titration of vanadium-containing germanium heteropolyacids with $CrSO_4$ solution. 2) Germanomolybdic, 3) undecomposed germanovanadotungstic, 4) germanovanadotungstic decomposed by boiling with alkali.

For the determination of the redox potential of germanotungstic acid, 50 ml concentrated hydrochloric acid and 1.41 ml $CrSO_4$ solution were added to 5 ml of the original heteropolyacid solution and the potential of the system obtained was measured (test Series I). As a check (in test Series II), 2.82 ml of $CrSO_4$ solution and 25 ml of concentrated hydrochloric acid were added to 5 ml of germanotungstic acid and the solution mixed with another solution containing an amount of Cr^{III} equivalent to 2.82 ml $CrSO_4$, 5 ml of germanotungstic acid and 25 ml of concentrated hydrochloric acid. The necessary amount of Cr^{III} solution was prepared by oxidizing an equal volume of $CrSO_4$ by heating in air. No blue color should be obtained on mixing the solutions of the trivalent chromium prepared and the germanotungstic acid. The results obtained in test Series I and II are given in Table 6.

The values obtained for the redox potential of the W^{VI}/W^{V} system with germanotungstic acid are considerably lower than the potential of the W^{VI}/W^{V} system where W^{VI} is not bound in a complex. The heteropolyanion apparently holds the W^{VI} so firmly that its concentration in the solution is infinitely small, while the concentration of W^{V} is measurable, the ratio $[W^{VI}]:[W^{V}]$ is almost zero, and the actual potential measured is that of the Cr^{III}/Cr^{II} system. The method described is evidently inapplicable to the determination of the redox potentials of tungsten heteropolyacids.

In an attempt to determine the potential of the germanotungstic acid – germanotungsten blue system it was found impossible to obtain the germanotungsten blue by ether extraction of the reduced heteropolyacid, since it is apparently oxidized or broken up in the extraction, in contrast to germanomolybdenum blue (the color of the aqueous solution after extraction was pale green).

The shape of the titration curves for germanotungstic acid with $CrSO_4$ solution also points to the very low stability of the reduced tungsten complex: the potential value would not fall so rapidly if the reduced tungsten was bound in a complex of stability comparable with that of the original heteropolycomplex.

It was established by qualitative tests that germanotungsten blue is more stable and more intensely colored in the absence of a large excess of sulfuric acid. Since, on the other hand, germanotungsten blue is only stable in the presence of excess reducing agent (as indicated by the impossibility of extracting it with ether), it was considered expedient to check whether a mixture of germanotungsten blue and excess divalent chromium would react stepwise during titration with potassium dichromate. It turned out, however, that the germanotungstic blue and the divalent chromium reacted simultaneously during titration without giving separate potential jumps. On adding excess $CrSO_4$ to a solution already oxidized with dichromate, the color became dark blue again, passing through green, evidently at the point when the excess dichromate had been reduced. Formation of the blue on reduction provides evidence that the heteropolyanion is not broken down by the processes described, since on addition of $CrSO_4$ to sodium tungstate or germanotungstic acid no blue is formed (cf. titration conditions for tungsten in heteropolyacid). The use of a more precise method of determining equivalence points (for example, amperometric titration) will possibly enable the composition of germanotungstic acid to be determined.

6. Redox Potentials of Germanovanadomolybdic and Germanovanadotungstic Heteropolyacids

Before proceeding to examine the results from the potentiometric titration of germanium heteropolyacids containing vanadium with $CrSO_4$ solution, we give the titration curve of ammonium vanadate with chromous sulfate solution. 10 ml 0.01935 N ammonium vanadate solution and 15 ml concentrated hydrochloric acid were taken for the titration, which was carried out in a carbon dioxide atmosphere (titration Curve 1 in Figure 3). It can be seen from the titration curve that V^{V} is reduced by $CrSO_4$ solution to V^{III}, giving two distinct potential jumps on reduction of V^{V} to V^{IV} and V^{IV} to V^{III}. The titration was carried out in the presence of hydrochloric acid, since molybdenum and tungsten were titrated under these conditions.

A. Titration of germanovanadomolybdic heteropolyacid. The titration of germanovanadomolybdic acid was carried out under the same conditions as the high temperature titration of germanomolybdic acid.

Titration was started immediately after the solution was decolorized, although the initial potential had not then been stabilized (evidently as a result of the very slow reduction of vanadium by hydrochloric acid). The titration curve is given in Figure 3 (Curve 2).

The titration curve of germanovanadomolybdic acid has three distinct potential jumps – at the equivalence points V^{V}/V^{IV}, Mo^{VI}/Mo^{V}, Mo^{V}/Mo^{III}. The jump corresponding to the equivalence point V^{IV}/V^{III} coincides with the jump Mo^{VI}/Mo^{V}.

Since germanovanadomolybdic acid contains the powerful oxidant pentavalent vanadium, it is reduced much more readily than germanomolybdic (for example in the synthesis process), and changes color from orange-red to pale blue even on the addition of a quantity of reducing agent sufficient to reduce only vanadium in the anion without reducing molybdenum. Its redox potential should obviously be determined first of all in the presence of vanadium, and not molybdenum, whose redox potential is equal to that of germanomolybdic acid.

For the determination of the redox potentials of germanovanadomolybdic acid, varying amounts of concentrated hydrochloric acid and $CrSO_4$ solution (the quantities of $CrSO_4$ solution were calculated as half of those necessary for the reductions V^{V} to V^{IV}, Mo^{VI} to Mo^{V}, Mo^{V} to Mo^{III}) were added to 2 ml of the original acid solution, and the potential of the systems obtained was measured at room temperature and after heating to 90° in a current of carbon dioxide. The potential values obtained are given in Table 7.

TABLE 7

Concentration of HCl in solution (N)	Volume of $CrSO_4$ solution (in ml)	Temperature	E_0 (relative to the hydrogen electrode, in V)
6	0.16	90°	+0.898
6	0.16	90	+0.902
6	1.40	90	+0.613
6	1.40	90	+0.618
6	3.74	90	+0.260
6	3.74	90	+0.260
6	0.16	22	+1.030
6	0.16	22	+1.043
6	1.40	22	+0.554
6	1.40	22	+0.568
6	3.74	22	+0.234
6	3.74	22	+0.230
0	0.16	22	+0.801
0	1.40	22	+0.358
0	3.74	22	+0.103

TABLE 8

Volume of $CrSO_4$ solution (in ml)	E_0 (relative to the hydrogen electrode, in V)
0.12	+0.879
0.12	+0.888
1.04	+0.236
1.04	+0.238

It follows from the results obtained that germanovanadomolybdic acid is a much more powerful oxidizing agent than germanomolybdic acid. Its potential after reduction of half the vanadium content is +1.036 V.

Germanovanadomolybdenum blue is much less stable in air than germanomolybdenum blue, so that the potential of the germanovanadomolybdic acid – blue system was not determined; it can hardly have any practical significance in analytical chemistry. The lower stability of the blue may be due to the fact that reduction of part of the molybdenum to Mo^{V} (as is necessary for formation of the blue) is accompanied by reduction of the vanadium to V^{III}, which is unstable in air and immediately begins to be reoxidized, catalytically accelerating the oxidation of molybdenum. On the other hand, in germanovanadomolybdic acid the molybdenum is isomorphously replaced by the vanadium, which occupies the place alloted to the former in the three-dimensional structure. On reduction, the ionic radius of part of the molybdenum ions is increased while the ionic radius of both vanadium ions is increased to a much greater extent; it is possible that these changes in ionic radii cannot be accommodated within the framework of the structure and the compound breaks down.

B. Titration of germanovanadotungstic heteropolyacid. In the titration of 1 ml of germanovanadotungstic acid in the presence of 25 ml of concentrated hydrochloric acid with $CrSO_4$ solution, it was found that a blue was formed at the start of the titration, as in the direct titration of germanotungstic acid, and the titration result is complicated by this circumstance (the ratio of the volumes of $CrSO_4$ solution used in the reduction of vanadium and molybdenum does not correspond to their actual concentrations, the potential jumps are indistinct). The titration Curve 3 is given in Figure 3. In subsequent experiments therefore the heteropolyacid was broken down by heating with 200 mg of solid caustic soda for 30 minutes, before titrating with $CrSO_4$ solution. The titration curve is given in Figure 3.

TABLE 9

$\frac{W^{VI}}{W^{V}}$		$\frac{Mo^{VI}}{Mo^{V}}$		Ge-Mo acid/ / blue	Ge-V-Mo acid/ /reduced form	Ge-V-W acid/ /reduced form
without complex	from Ge-W acid	without complex	from Ge-Mo acid			
+ 0.208	+ 0.040	+ 0.625	+ 0.540	+ 0.703	+ 1.036	+ 0.833

As the titration results show, V^{V} and W^{VI} react separately, giving two distinct potential jumps at the equivalence points V^{V}/V^{IV} and W^{VI}/W^{V}; the second vanadium jump (V^{IV}/V^{III}) coincides with the W^{VI}/W^{V} jump.

For the determination of the redox potentials of germanovanadotungstic acid, 25 ml of concentrated hydrochloric acid and different amounts of $CrSO_4$ solution (half the amounts required for titration to the jumps V^{V}/V^{IV} and W^{VI}/W^{V}) were added to 1 ml of undecomposed heteropolyacid and the potentials of the systems obtained were measured at room temperature (Table 8).

From this, the redox potential of germanovanadotungstic acid in the presence of conc. HCl at room temperature may be taken as + 0.883 V. This potential is evidently a property of the complex itself and is not due to the presence of pentavalent vanadium in the solution, otherwise the potentials of germanovanadomolybdic and germanovanadotungstic acids would be identical.

The values of the W^{VI}/W^{V} potentials in germanovanadotungstic acid (+ 0.238 V) are close to the values in sodium tungstate (+0.206 V); as a result, the complex breaks down on further reduction.

The values of the redox potentials obtained for the systems studied are given in Table 9.

The following data on redox potential values for the Mo^{VI}/Mo^{V} and W^{VI}/W^{V} systems are given in the literature: Collenberg and Guthe [7] calculated that $E_{f}W^{VI}/W^{V} = + 0.261$ V. The same value was also obtained experimentally by Yu. A. Chernikhov and V. G. Goryushina [1]. El-Shamy and Tourky [8] found for the $Mo^{VI}/$ $/Mo^{V}$ system in 8 N HCl $E_{f} = + 0.470$ V. El-Shamy and El-Aggan [9] give the value + 0.4825 V for $E_0\ Mo^{VI}/Mo^{V}$.

Tourky, Issa and Amin, in a study of the possibility of using pentavalent tungsten in analysis, give the following values for $E_{f}W^{VI}/W^{V}$:

Concentration of HCl in the solution (N)	10.5	10.5	9.0	8.0	7.0
$E_{f}W^{VI}/W^{V}$	0.247	0.216	0.155	0.108	0.065

The individual discrepancies between the data obtained by us and those given in the literature may be explained by differences in experimental conditions and different accuracy in measurement.

SUMMARY

1. The redox potentials of tungsten and molybdenum are lowered in heteropolycompounds, as is general in complex formation.

2. High redox potential is a property not of Mo^{VI} or W^{VI} bound in the complex, but of the whole complex heteropolyanion, which on reduction gives a blue colored heteropolyanion containing a definite amount of molybdenum or tungsten reduced to the pentavalent state.

3. In studying the redox potentials of all the heteropolycompounds it is necessary first of all to examine the redox potentials of the heteropolyacid-heteropoly blue systems.

4. The introduction of vanadium into the molecules of the heteropolycompounds raises considerably the redox potentials of the latter.

5. A more detailed study of the redox properties of heteropolycompounds may widen the field of their use as redox indicators in analysis.

LITERATURE CITED

[1] Yu. A. Chernikhov and V. G. Goryushina, Factory Labs. 11, 137 (1945).

[2] A. I. Busev, J. Anal. Chem. 6, 178 (1951).

[3] R. Berg, The Use of o-Hydroxyquinoline in Analytical Chemistry (State Sci-Tech. Press, Moscow, 1937).

[4] V. G. Goryushina and V. G. Cherkashina, Factory Labs. 14, 255 (1948).

[5] Yu. A. Chernikhov and V. G. Goryushina, Factory Labs. 12, 397 (1946).

[6] A. M. Dymov, The Technical Analysis of Ores and Metals (Metallurgical Press, Moscow, 1949).

[7] C. Collenberg and A. M. Guthe, Z. Allg. anorg. Chem. 136, 252 (1924).

[8] A. K. Tourky and H. K. El-Shamy, J. Chem. Soc., 1949, 140.

[9] H. K. El-Shamy and A. M. El-Aggan, J. Am. Chem. Soc., 75, 1187 (1953).

[10] A. K. Tourky, I. M. Issa, and A. M. Amin, Anal. Chim. Acta 10, 168 (1954).

Received July 10, 1955

Moscow State University

THE INTERACTION OF SOME LITHIUM AND CADMIUM SALTS IN THE ABSENCE OF SOLVENT

D. S. Lesnykh, A. G. Bergman and N. G. Bukun

The influence of the nature of cations on the mutual solubility of melt components, with reference to electronic structure and polarizability in the light of the position of the elements in the periodic system of D. I. Mendeleev, has been pointed out earlier [1].

To clarify the influence of the nature of certain anions on the mutual solubility of the components and the displacement of equilibrium in melts, we made a study of the reciprocal system from lithium and cadmium chlorides and molybdates, and also of the diagonal sections of the reciprocal systems from the chlorides and orthovanadates, and from the chlorides and tungstates of lithium and cadmium. The examination was made by the visual-polymetric method.

Diagonal Sections of the Li, Cd || Cl, MoO_4 system

As a result of the reversibly-reciprocal character of the system there are branches corresponding to exchange products on the fusion diagrams of both diagonal sections (Figure 3). Thus the fusion curve for the section $CdCl_2$–Li_2MoO_4 consists of three crystallization branches: $CdCl_2$, $CdMoO_4$ (exchange product) and Li_2MoO_4, intersecting respectively at 523° and 8%, 492° and 38.5% lithium molybdate, while the fusion curve Li_2Cl_2–$CdMoO_4$ consists of five branches: α, β-LiCl, β, α-Li_2MoO_4 (exchange product) and $CdMoO_4$, intersecting respectively at 562° and 12.5%, 474° and 27.5%, 514° and 37%, 541° and 50% cadmium molybdate.

TABLE 1

Binary Systems (Figure 1)

System	Characteristic points of the curve	Coordinates of the characteristic points	
		mole %	melting point
$Li_2Cl_2 \longrightarrow CdCl_2$	Uninterrupted series of solid solutions with miniumum; α, β-transition LiCl	78	500*
$Li_2Cl_2 \longrightarrow Li_2MoO_4$	Eutectic;	41	498
	α, β-transition LiCl;		558
	LiCl;		
	β-transition		518
	Li_2MoO_4		
$Li_2MoO_4 \longrightarrow CdMoO_4$	Eutectic	19.5	654
$CdCl_2 \longrightarrow CdMoO_4$	Eutectic	4.5	553

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* The same coordinates are given by S. D. Gromakov [2].

The reciprocal system Li, Cd || Cl, MoO_4. The crystallization surface was studied from seven internal sections, whose directions are shown in Figure 4; brief characteristics of each of them are given in Table 2, the results obtained are presented in the form of a projection of the isothermals on the composition square of the reci-

TABLE 2

Sections of the Reciprocal System Li, Cd ‖ Cl, MoO_4

Section Nos.	Original components of the mixture	Melting point of original mixture	Component added	Branches of the		
				branch 1	intersection of branches 1 and 2	
					%	t°
I	25% Li_2Cl_2 + 75% $CdCl_2$ . .	503°	$CdMoO_4$	[Li,Cd]Cl	16.5	476
II	40% Li_2Cl_2 + 60% $CdCl_2$ . .	518	$CdMoO_4$	[Li,Cd]Cl	23.0	442
III	50% Li_2Cl_2 + 50% $CdCl_2$ . .	527	$CdMoO_4$	[Li,Cd]Cl	22.0	444
IV	75% Li_2Cl_2 + 25% $CdCl_2$ . .	571	$CdMoO_4$	[Li,Cd]Cl	22.0	466
V	70% Li_2Cl_2 + 30% Li_2MoO_4 .	542	$CdCl_2$	[Li,Cd]Cl		
VI	25% $CdMoO_4$ + 75% Li_2MoO_4	713	Li_2Cl_2	$CdMoO_4$	7.0	642
VII	50% $CdMoO_4$ + 50% Li_2MoO_4	930	Li_2Cl_2	$CdMoO_4$	26.0	592

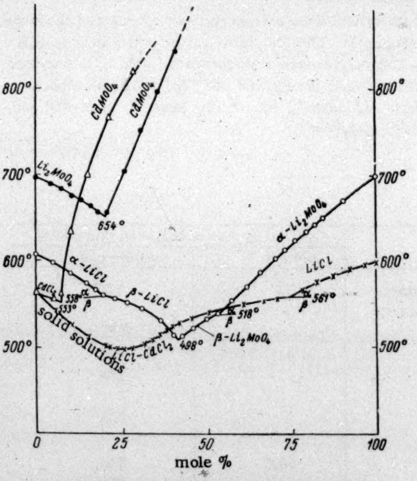

Fig. 1. Fusion diagrams of the binary systems: $Li_2Cl_2-CdCl_2$; $Li_2Cl_2-Li_2MoO_4$; Li_2MoO_4; $Li_2MoO_4-CdMoO_4$; $CdCl_2-CdMoO_4$.

procal system (Figure 2). In Figure 5 the projection of the invariant points and the lines of joint crystallization of the components on the $Li_2Cl_2-CdCl_2$ side is drawn.

The crystallization surface of the system consists of five fields: α, β-solid solutions [Li, Cd] Cl (23.2% of the area of projection); α, β-Li_2MoO_4 (31.4%) and $CdMoO_4$ (45.5%). The point E corresponds to a triple eutectic of composition 8% Li_2Cl_2, 24.5% Li_2MoO_4 and 67.5% $CdCl_2$, melting at 434°, as is seen from Figure 2.

Diagonal Sections of the Li, Cd ‖ Cl, VO_4 system

The stable section $(CdCl_2)_3-(Li_3VO_4)_2$ forms a system with eutectic at 464° and 15% lithium orthovanadate.

The fusion curve of the unstable section $(LiCl)_6-Cd_3(VO_4)_2$ consists of three crystallization branches LiCl, Li_3VO_4 and $Cd_3(VO_4)_2$, intersecting respectively at 590° and 3.5%, 710° and 58% cadmium orthovanadate (Figure 6).

From the character of the diagonal sections the reciprocal system appears irreversibly-reciprocal.

Diagonal Sections of the Li, Cd ‖ Cl, WO_4 system

The stable section $Li_2Cl_2-CdWO_4$ has the characteristics of a binary system with eutectic at 493° and 26% $CdWO_4$. For $CdWO_4$ α, β, γ-

TABLE 2 (continued)

crystallization curves and their intersections										Coordinates of maxima on the curves	
branch 2	intersection of branches 2 and 3		branch 3	intersection of branches 3 and 4		branch 4	intersection of branches 4 and 5		branch 5	%	t°
	%	t°		%	t°		%	t°			
$CdMoO_4$											
$CdMoO_4$											
β-Li_2MoO_4	29.0	476	$CdMoO_4$								
β-Li_2MoO_4	37.5	512	α-Li_2MoO_4	42.0	530	$CdMoO_4$					
α-Li_2MoO_4	55.0	512	β-Li_2MoO_4	64.0	493	β-LiCl	81.0	562	α-LiCl	10	642
α-Li_2MoO_4	58.5	508	β-Li_2MoO_4	66.5	485	β-LiCl	83.5	562	α-LiCl	32	595

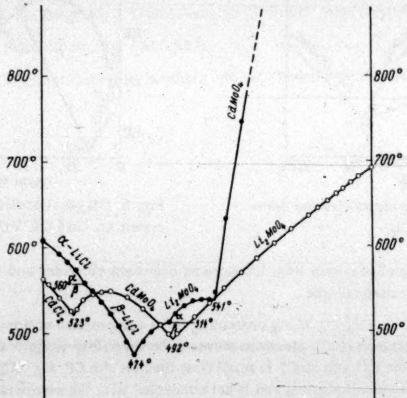

Fig. 2. Projection of the isothermals on the composition square of the reciprocal system Li, Cd‖ Cl, MoO_4.

transitions are observed at 562 and 750°. At 558° an α, β-transition of lithium chloride takes place (Figure 7).

The greater part of the fusion curve of the $LiWO_4-CdCl_2$ section is occupied by the exchange product α, β-$CdWO_4$, intersecting the crystallization branches of Li_2WO_4 at 690° and 17.5%, and of $CdCl_2$ at 550° and 97% of the latter.

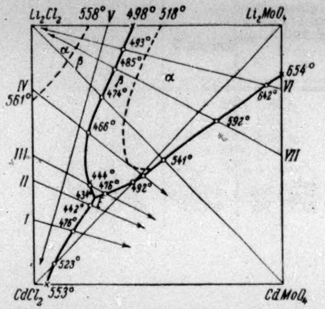

Fig. 3. Diagonal sections of the reciprocal system Li, Cd ‖ Cl, MoO_4.

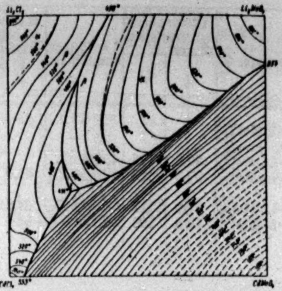

Fig. 4. Positions of the internal sections of the reciprocal system Li, Cd ‖ Cl, MoO_4.

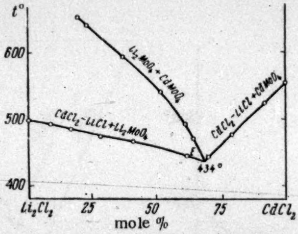

Fig. 5. Projection of the crystallization diagrams on the LiCl−$CdCl_2$.

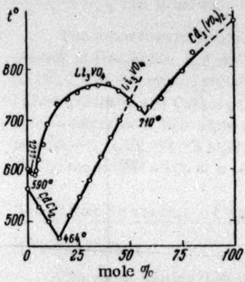

Fig. 6. Diagonal sections of the reciprocal system Li, Cd ‖ Cl, VO_4.

In contrast to the reciprocal system from lithium and cadmium chlorides and molybdates the above system belongs to the irreversibly-reciprocal type.

The reciprocal system Li, Cd ‖ Cl, MoO_4 containing in its composition cations with external electronic structures of two ($Li^{\cdot}$) and eighteen ($Cd^{\cdot\cdot}$) electrons proves to be reversibly-reciprocal, evidently because the difference in polarizability of the Cl' and MoO_4'' is small (less than for the Cl' and SO_4'' ions, present in the system Li, Cd ‖ Cl, SO_4 which separates into layers) and is not connected with the comparatively large difference in polarizability of the cadmium and lithium cations [3].

Considering the irreversibly-reciprocal character of the Li, Cd ‖ Cl, WO_4 and Li, Cd ‖ Cl, VO_4 systems and the opposite direction of the exchange reaction in these systems it may be assumed that the WO_4'' anion has greater polarizability than the VO_4''' anion. Thus the anions considered fall in the order

with reference to the magnitude of their polarizability coefficients.

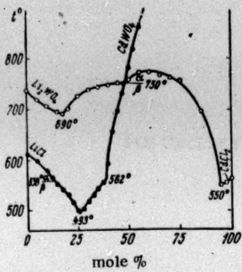

Fig. 7. Diagonal sections of the reciprocal system Li, Cd ‖ Cl, WO_4.

The exchange reaction in melts often goes in the direction of the formation of the salts with ions of greatest polarizability and the salts with the ions of least polarizability, especially if the cations and anions differ considerably in polarizability between themselves. In this case the polarizability of the ions is the factor determining the direction of the exchange reaction. The large difference in polarizability of the anions in conjunction with the large difference in polarizability of the cations is one of the conditions for the sharp equilibrium displacement up to separation of the layers in the molten state.

SUMMARY

1. The ternary reciprocal system from the chlorides and molybdates of lithium and cadmium, and the diagonal sections of the reciprocal systems from the chlorides and orthovanadates, and from the chlorides and tungstates of lithium and cadmium have been studied by the visual-polymetric method.

2. For the same cation composition, the irreversibility of the exchange reaction increases and the mutual solubility in the melts decreases with increase in the difference in polarizability of the anions.

3. A large difference in polarizability of the anions in conjunction with a large difference in polarizability of the cations is one of the conditions for the sharp displacement of equilibrium in the direction of the formation of the salts with ions of greatest polarizability and the salts with ions of least polarizability.

LITERATURE CITED

[1] D. S. Lesnykh and A. G. Bergman, J. Gen. Chem. 23, 373, 537, 894 (1953) (T.p.383, 557, 935).*

[2] S. D. Gromakov, J. Phys. Chem. 24, 500 (1950).

[3] B. V. Nekrasov, A Course of General Chemistry, 9th ed. (Moscow-Leningrad, 1952).

Received May 31, 1955

Rostov-on-Don State University

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* T.p = C. B. Translation pagination.

SOLUBILITY IN THE POTASSIUM CHLORIDE – UREA – WATER SYSTEM AT 25°

A. K. Zhdanov and K. G. Nigai

Solubility in the urea – potassium chloride – water system has been studied by the visual-polymetric method in the region between −19.4° and +40° [1] and in the region from +25° to the freezing point of the system [2]. The present work was devoted to a study of the solubility in the system mentioned at 25° by the isothermal method.

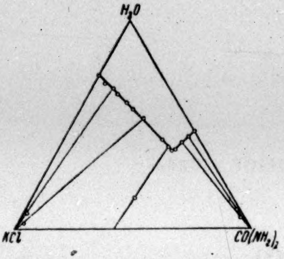
Solubility in the System $KCl-CO(NH_2)_2-H_2O$ at 25°

Density (g/ml)	Composition of solution (%)			Composition of residue (%)			Solid phase
	KCl	$CO(NH_2)_2$	H_2O	KCl	$CO(NH_2)_2$	H_2O	
1.1768	26.16	—	73.84	—	—	—	KCl
1.1830	25.04	4.90	70.06	—	—	—	
1.1874	23.96	9.04	67.00	91.31	1.10	7.59	
1.1923	23.20	12.17	64.63	—	—	—	
1.1987	21.76	17.38	60.86	—	—	—	
1.2057	20.27	22.67	57.06	—	—	—	
1.2155	18.15	29.16	52.69	95.96	1.70	2.34	
1.2298	15.65	41.68	42.67	—	—	—	
1.2395	14.21	46.87	38.92	42.18	43.23	14.59	$KCl + CO(NH_2)_2$
1.2406	14.15	47.60	38.25	—	—	—	
1.2400	14.11	47.10	38.80	—	—	—	
1.2401	14.11	47.58	38.31	—	—	—	
1.2257	13.02	47.95	39.03	—	—	—	$CO(NH_2)_2$
1.2029	8.25	49.94	41.81	0.88	94.23	4.89	
1.1534	4.21	52.05	43.74	0.94	90.65	8.41	
1.1503	—	53.10	46.90	—	—	—	$CO(NH_2)_2$

The method of preparing the saturated solutions has been described earlier [3]. The potassium chloride content in the solution samples and in the moist residue was obtained by potentiometric titration with 0.1 N $AgNO_3$, the urea content by the bromometric method [4]. The water content was found by difference. The results obtained are given in the table and plotted in the diagram.

It is seen from the data in the table that the solubility of potassium chloride decreases on addition of urea to a saturated solution of the former, while the solubility of urea decreases on addition of potassium chloride to a saturated solution of urea. The density of the saturated solutions increases both on addition of urea to the potassium chloride solution and on addition of potassium chloride to the urea solution, and reaches its highest value at the eutectic point (1.2406 g/ml).

Inspection of the Gibbs triangular diagram (in figure) shows that the solid phases in the system are: potassium chloride for solutions saturated with potassium chloride, urea for solutions saturated with urea and a mixture of both for the eutectic point.



Isothermal section of the composition diagram of the system $KCl - CO(NH_2)_2 - H_2O$ at 25°.

SUMMARY

1. The determination of the solubility and solution density of the potassium chloride – urea – water system at 25° has been carried out by the isothermal method.

2. The potassium chloride – urea – water system belongs to the simplest type in which no formation of molecular compound or of solid solution takes place.

LITERATURE CITED

[1] V. A. Polosin and R. K. Ozolin, J. Gen. Chem. 17, 403 (1947).

[2] I. M. Bokhovkin and Yu. I. Bokhovkina, J. Gen. Chem. 17, 621 (1947).

[3] A. K. Zhdanov and K. G. Nigai, J. Gen. Chem. 26, 2134 (1956).

[4] I. M. Kolthoff, Volumetric Analysis (State Chem. Press, 1932),615.

Received November 21, 1955

Mid-Asia State University

THE INFLUENCE OF ALKALI METAL CATIONS IN COMPLEX COMPOUNDS OF ALUMINUM BROMIDE ON THE MOLECULAR COMPOSITION OF THESE COMPLEXES IN SOLVENTS OF LOW DIELECTRIC CONSTANT

E. Ya. Gorenbein

In the study of electrolyte solutions attention is chiefly directed to the chemical interaction taking place between the components of the system and to the influence of the medium on the degree of electrolytic dissociation of the electrolyte on transfer from a solvent of high dielectric constant to a solvent of lower DC.

The phenomenon of association of an electrolyte, whereby its molecular weight is higher than that given by the molecular formula, has been interpreted as autocomplex formation followed by electrolytic dissociation into complex ions [1].

Our studies of concentrated solutions of electrolytes have shown that the decrease in molecular conductivity with dilution, corrected for viscosity, starts from the isolated liquid electrolyte [2]. This phenomenon was interpreted by us on the basis of contemporary theory of the liquid state [3]. Taking into consideration the fact that the increase in molar conductivity with increase in concentration is related to the increase in association of the electrolyte, and that the association coefficient is not of constant magnitude, we put forward the suggestion that the limiting value of the degree of association of the electrolyte in the solution corresponds to the association of the isolated electrolyte in the liquid state [4]. The phenomenon of association of an electolyte is simply the manifestation of the degree of order of its molecules in the solution. The degree of order of an electrolyte in solution should be influenced not only by the electrolyte concentration but also by the dielectric constant of the medium, i.e., to obtain the same molecular composition of an electrolyte in solution we may either increase the electrolyte concentration (in solvents of high DC) or decrease the dielectric constant of the medium by using a solvent of low DC [5]. If our suggestion is correct, i.e., if the increase in molecular weight with increase in electrolyte concentration is the result of the formation of structural groups consisting of the different ions interacting according to the laws governing the formation of ionic lattices, and that these structural groups behave in cryoscopic studies as separate kinetic particles, it would be expected that study of the molecular composition of electrolytes with different cations of varying polarizability should reveal a varying degree of order (association) of the electrolytes in solvents of low DC.

To verify this, we undertook a cryoscopic study of benzene solutions of aluminum complexes obtained by fusing alkali metal halides with aluminum bromide.

EXPERIMENTAL

Starting materials and working method. The synthesis of aluminum bromide has been described earlier [6]. The alkali metal halides were purified by recrystallization. The sodium and potassium chlorides were ignited, while the lithium chloride was dehydrated in a current of hydrogen chloride and stored in sealed ampoules. The sodium and lithium iodides were dehydrated in a current of hydrogen and stored in the same way as lithium chloride. The potassium iodide, after careful purification and drying, was stored in a desiccator over P_2O_5. The cryoscopic benzene was dried and redistilled from metallic sodium. A sample distilling at a fixed temperature was used for the work.

The complexes were prepared by fusing the aluminum bromide with the alkali metal halides. They had the composition $MeHal \cdot 2AlBr_3$. The cryoscopic measurements were made using a Beckmann apparatus adapted for use with hygroscopic materials. The lowering of the freezing point was determined using a Beckmann thermometer. The solution was stirred by a platinum stirrer driven by an electromagnet with switch.

Measurement results. The aluminum bromide complexes were fused in the cryoscopic vessel and weighed, after which the appropriate amount of benzene was added. The freezing point measurements were repeated at least three times and the mean value taken.

Solutions of the following complexes were studied: $KCl \cdot 2AlBr_3$, $KI \cdot 2AlBr_3$, $NaCl \cdot 2AlBr_3$, $NaI \cdot 2AlBr_3$, $LiCl \cdot 2AlBr_3$ and $LiI \cdot 2AlBr_3$.

The complex compounds of rubidium and cesium halides with aluminum bromide could not be studied because of their extremely low solubilities in benzene. The data for solutions of the complex compounds of potassium, sodium and lithium bromides with $AlBr_3$ were taken from [7]; however, the last value (the most concentrated solution) for the $NaBr \cdot 2AlBr_3$ complex was determined by us.

The results of measurements on the complex compounds with alkali metal chlorides are given in Tables 1-3, while the remaining data are presented graphically.

TABLE 1

The System $KCl \cdot 2AlBr_3 - C_6H_6$.

Concentration of complex (mole %)	Freezing point lowering	Calculated molecular weight	Degree of association (i)
3.24	0.39°	3422	5.63
2.53	0.37	2790	4.59
2.02	0.35	2352	3.87
1.66	0.33	2039	3.35
0.87	0.26	1140	2.20
0.77	0.24	1284	2.11
0.71	0.23	1246	2.05

TABLE 2

The System $NaCl \cdot 2AlBr_3 - C_6H_6$

Concentration of complex (mole %)	Freezing point lowering	Calculated molecular weight	Degree of association (i)
2.93	0.50°	2343	3.96
2.43	0.48	2015	3.40
2.07	0.46	1780	3.01
1.33	0.44	1187	2.01
1.17	0.42	1091	1.84

TABLE 3

The System $LiCl \cdot 2AlBr_3 - C_6H_6$

Concentration of complex (mole %)	Freezing point lowering	Calculated molecular weight	Degree of association (i)
3.85	1.58	957	1.66
2.93	1.35	844	1.46
2.39	1.13	817	1.42
1.85	0.95	750	1.30
1.67	0.88	729	1.27
1.57	0.84	718	1.25
1.51	0.82	705	1.22
1.31	0.78	642	1.12
1.28	0.74	634	1.10

The curves in Figure 1 show the relationship between the degree of of association (i) of the electrolyte and the concentration of the components expressed as mole %.

From the data presented it is seen that the degree of association shows a linear dependence on the electrolyte concentration for the concentration range studied, and that the greatest association is undergone by the complex containing the potassium ion in its outer sphere irrespective of the halogen with which the potassium was combined before the formation of the complex compound.

Replacement of the chloride by the bromide or iodide of the alkali metal before formation of the complex compound has little influence on the degree of association of these electrolytes, which shows that the complexes studied have identical structures.

It is possible that at the concentrations studied a certain deviation from the accurate degree of association values takes place, but nevertheless the fact that the degree of association of the electrolytes mentioned increases with increase in concentration cannot be doubted.

DISCUSSION OF RESULTS

The existence of complex compounds of aluminum bromide with the alkali metal bromides, of composition $MeBr \cdot 2AlBr_3 (Me = Li, Na, K)$, and of similar compounds with potassium chloride has been established by thermal analysis [8, 9]. Compounds of the remaining halides were prepared by analogy. The aluminum bromide underwent no exchange with the alkali metal chlorides in benzene solution, for when exchange takes place aluminum chloride should be precipitated as it is insoluble in benzene. (Exchange has been observed in the $AlBr_3 - SbCl_3 - C_6H_5Cl$ system in which $AlCl_3$ is precipitated [10].) Exchange takes place between the alkali metal iodides and

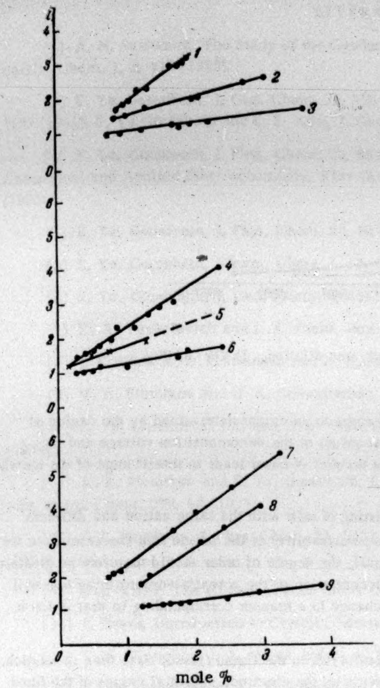


Fig. 1. Relation between degree of association of complex compounds and their concentration in solution.

1) $KI \cdot 2AlBr_3$, 2) $NaI \cdot 2AlBr_3$, 3) $LiI \cdot 2AlBr_3$, 4) $KBr \cdot 2AlBr_3$, 5) $NaBr \cdot 2AlBr_3$, 6) $LiBr \cdot 2AlBr_3$, 7) $KCl \cdot 2AlBr_3$, 8) $NaCl \cdot 2AlBr_3$, 9) $LiCl \cdot 2AlBr_3$.

aluminum bromide. This is shown by the cherry-red color of the solutions and also by a decrease in the degree of association of these complexes. Other conditions being equal, the complexes of $AlBr_3$ with alkali metal iodides bring about a greater lowering of the freezing point of the solutions, which is related to the increase in the number of particles as a result of exchange.

In the complex compounds studied by us the aluminum ion is the complex former. The coordination numbers of aluminum are chiefly 4 and 6. From this the structure of the complex compounds studied can be taken as $Me[Al(Hal)_4] \cdot AlBr_3$. Compounds of such composition are found in the literature [11]. Their structure agrees with decomposition potential data: on electrolysis of solutions of the electrolytes mentioned the corresponding alkali metals may be isolated at the cathode [12]; the alkali metal cation therefore lies in the outer sphere of the complexes studied, while the anion forms a fairly stable unit.

The change in degree of association of the complex compounds on changing from an alkali metal cation of smaller atomic weight to a cation with greater atomic weight shows that the cause of this phenomenon lies in the nature of the cation. The formation of structural groups depends on the nature of both cation and anion. In this case the nature of the anion is unaltered. Here, evidently, two factors are involved: the change in cation radius and the polarizability of the ion [13]. It is known that the polarizability of the alkali metal cations increases from lithium to cesium [14] while their radii increase simultaneously. These factors act in opposite directions in the formation of structural groups involving alkali metal cations. Experimental evidence shows that complexes containing potassium ions are more associated than complexes containing sodium ions, while the latter are more associated than complexes containing lithium ions, thus indicating the predominating influence of the degree of polarizability. At this point, however, it is necessary to study the degree of solvation of the cations.

In Figure 2 the relationship between the molar conductivity (μ) of three complex compounds $LiBr \cdot Al_2Br_6$ [15], $NaBr \cdot Al_2Br_6$ and $KBr \cdot Al_2Br_6$ [6] and the dilution (φ) is shown. The highest molar conductivity is shown by the complex $KBr \cdot Al_2Br_6$ and the lowest by $LiBr \cdot Al_2Br_6$ in the region of moderate concentration. Since in these compounds the structure of the anion is the same it must be assumed that the decrease in conductivity of these compounds is related to the different degree of solvation of the cations – by increasing the radius of the lithium ion, while this in turn weakens the force of interaction between the ions and also reduces the degree of association of the electrolyte. The increase in polarizability of the ions leads to a greater degree of order in the solution. It should be noted that other authors [7] have already pointed out the influence of the polarizing power of the alkali metal cations in these solutions, but they started from the point of view of complex compound stability, and not the formation of structural units.

Thus the data presented confirm our view that the observed association of electrolytes in solvents of low DC is simply the manifestation of the degree of order, characterized by the presence of structural groups which behave in cryoscopic determinations as separate kinetic particles. At the same time our suggestion that the phenomenon of association (order) should influence the electrochemical properties of these solutions has been confirmed [16].

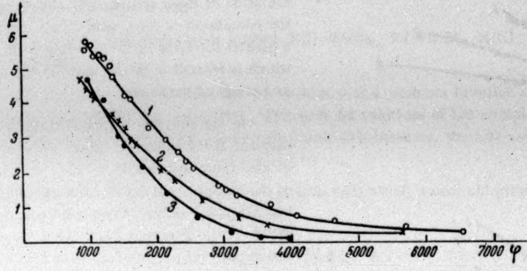


Fig. 2. Relationship between molar conductivity and dilution. 1) $KBr \cdot 2AlBr_3$, 2) $NaBr \cdot 2AlBr_3$, 3) $LiBr \cdot 2AlBr_3$.

The concentration of the potential-determining ions changes to an extent determined by the degree of association of the electrolyte, and consequently the numerical values of the decomposition voltage and the magnitude of the electrode potentials also change, which in a number of cases leads to interchange of the metals in the voltage series [17].

Such a picture should also be observed for systems consisting of salts with the same cation and different anions having different polarizability. It is known that the polarizability of the halide ions increases from the fluoride ion to the iodide ion [14]. Other conditions being equal, the degree of order should therefore be greatest for electrolytes with the iodide ion. For such solutions the concentration of the potential-determining ions will be less, and as a result the electrode potential values should change in a manner corresponding to that which is in fact observed [18].

A much greater degree of order is shown by isolated electrolytes in the liquid (fused) state than in solution. As a result, the influence of the degree of order in the electrolyte on the electrode potential values of the fused isolated salts on replacement of the chloride ion by bromide or iodide ions should naturally be much more pronounced. The accuracy of this conclusion is illustrated by data given in a work by P. F. Antipin and co-authors [19].*

It is of course the case that the formation of structural groups is influenced not only by the polarizability of the ions but also by other properties of the components, including the ionic radius, so that deviations from this regularity often occur in solutions.

SUMMARY

1. Cryoscopic studies of the complexes $KCl \cdot Al_2Br_6$, $NaCl \cdot Al_2Br_6$, $LiCl \cdot Al2Br_6$, $KI \cdot Al_2Br_6$, $NaI \cdot Al_2Br_6$ and $LiI \cdot Al_2Br_6$ in benzene have been carried out.

2. It has been established that the degree of order (association) of the electrolytes depends linearly on the concentration of the components (in mole %) and is increased on replacing an alkali metal cation of lower atomic weight by an alkali metal cation of higher atomic weight in the complex compound.

3. A connection has been shown between the change in degree of order in an electrolyte with changing concentration and the electrode potential values in solvents of low DC.

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[*] In this connection the statement by Yu. K. Delimarksy . . ."First of all the influence of the anion on the electrode potential was established, namely, that on changing from the chlorides to the bromides and iodides the potentials of the same metals become more negative" [20] appears rather strange; while this fact has long been known, it has received no suitable explanation.

LITERATURE CITED

[1] A. N. Sakhanov, The Study of the Conductivity of Nonaqueous Solutions (1913); M. A. Rabinovich, Ukrain. Chem. J. 3, 418 (1928).

[2] E. Ya. Gorenbein, J. Gen. Chem. 15, 729 (1945); 17, 873 (1947); J. Phys. Chem. 20, 881 (1946); 25, 1160 (1951); E. Ya Gorenbein and E. E. Kriss, J. Gen. Chem. 21, 1387 (1951); J. Phys. Chem. 26, 346 (1952).

[3] E. Ya. Gorenbein, J. Phys. Chem. 20, 881 (1946); The Work of the Second All-Union Conference on Theoretical and Applied Electrochemistry, Kiev (Acad. Sci. USSR Press, 1949) 304; Ukrain. Chem. J. 16, 107 (1950).

[4] E. Ya. Gorenbein, J. Phys. Chem. 20, 547 (1946).

[5] E. Ya. Gorenbein, Ukrain. Chem. J. 16, 107 (1950).

[6] E. Ya. Gorenbein, J. Gen. Chem. 9, 2041 (1939).

[7] Z. A. Yankelevich and I. A. Sheka, Rep. Inst. Chem. Acad. Sci. USSR, 5, 59 (1938).

[8] J. Kendall, E. D. Crittenden and H. K. Miller, J. Am. Chem. Soc. 45, 963 (1923).

[9] V. A. Plotnikov and U. A. Schwartzman, J. Phys. Chem. 12, 120 (1938).

[10] E. Ya. Gorenbein, Sci. Rep. Kiev State Univ. 3, v. 3, (chem. coll.), 175 (1937); J. Gen. Chem. 8, 233 (1938).

[11] V. A. Plotnikov and E. Ya. Gorenbein, J. Gen. Chem. 5, 1108 (1935); G. Jander and W. Zschaage, Z. allg. anorg. Chem. 272, 53 (1953).

[12] S. I. Yakubson, J. Phys. Chem. 21, 343 (1947); M. E. Lerner and O. K. Kudra, J. Phys. Chem. 28, 1006 (1954).

[13] Van-Arkel, The Chemical Bond (State Chem. Press, 1934), 54, 62.

[14] R. Evans, Introduction to Crystal Chemistry (State Chem. Press, 1948), 178.

[15] V. A. Plotnikov, I. A. Sheka and Z. A. Yankelevich, J. Gen. Chem. 3, 481 (1933).

[16] E. Ya. Gorenbein and I. M. Slavutskaya, J. Gen. Chem. 8, 1169 (1938).

[17] E. Ya. Gorenbein, J. Gen. Chem., 26, 2107 (1956); First Ukrainian Republican Conference on Physical Chemistry, Kiev (Acad. Sci. USSR Press, 1954), 67.

[18] V. A. Izbekov and E. M. Skobets, Rep. Inst. Chem. Acad. Sci. USSR, 4, 85 (1937).

[19] P. F. Antipin, A. F. Alabyshev, B. P. Artamonov and V. P. Barzakovsky, The Electrochemistry of Fused Salt (State Sci-Tech. Press, 1937), 187, Moscow-Leningrad.

[20] Yu. K. Delimarsky, Studies on the Chemistry of Solutions and Complex Compounds (Acad. Sci. USSR Press, Kiev, 1954), 47.

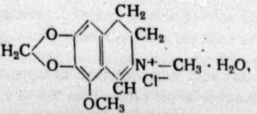
Received November 1, 1955

Kiev Veterinary Institute

THE POLAROGRAPHIC BEHAVIOR OF STYPTICIN. I

N. Ya. Khlopin and G. F. Reikhardt

The chloride of the alkaloid cotarnine (N-methyl-6,7-methylenedioxy-8-methoxy-3,4-dihydroisoquinoline chloride),



known as stypticin, is widely used in medicine as a valuable hemostatic agent [1-3].

It is known that chemical methods of alkaloid analysis, in both raw materials and finished pharmaceutical products, taking into account their low concentrations, are among the most difficult in pharmaceutical analysis, so that there is both theoretical and practical interest in establishing a possible use of the polarographic method for these cases.

It has been shown [4-6] that only a few alkaloids are reduced at the dropping mercury electrode, the majority not being reduced by this means. The polarographic waves which they give are apparently obtained as a result of the catalytic liberation of hydrogen.

Our aim was to study the polarographic behaviour of stypticin and in particular to examine the conditions for its reduction at the dropping mercury electrode.

EXPERIMENTAL

The polarographic studies were carried out by the visual method. A mirror galvanometer of sensitivity $2 \cdot 10^{-9}$ A was used. The capillary used had the characteristic values $m^{2/3} = 1.9663$ and $\tau^{1/6} = 1.1224$ (the geometrical characteristics were obtained with 0.1N potassium chloride solution at 0.0 V, mercury column pressure 27.3 cm and mercury drop interval 2 seconds). No rubber tubing was used to connect the capillary to the mercury reservoir.

The following buffer solutions were prepared: acetate buffers with pH 2.61, 3.91, 5.08 and phosphate-borate buffers with pH 6.25, 6.83 and 8.02. The pH of the solutions was checked using a hydrogen electrode. To prevent change in the pH of the buffer solutions on storage, the insides of the flasks were covered with paraffin. Standard 0.0148 M stypticin solution was prepared from the salt checked for purity according to [7]. The working solutions were prepared by diluting this standard solution.

For the polarographic work, 1 ml of working solution of stypticin and 1 ml of buffer solution were measured into the electrolysis cell using a microburet. A current of pure nitrogen was passed through the test solution for 20 minutes to remove dissolved oxygen. In fixing the height of the polarographic wave the magnitude of the residual current was taken into account, for which a polarographic examination of one of the buffer solutions was carried out at the same time.

The results of the measurements are given in the Table.

Magnitude of Limiting Current of Stypticin at Different pH, in Microamperes

Concentration (mmol./l)	pH					
	2.61	3.91	5.07	6.25	6.83	8.02
0.117	1.40	1.00	1.00	1.20	0.80	1.40
0.235	2.60	1.80	2.20	2.40	2.00	2.20
0.622	2.60	2.80	3.40	3.40	2.80	3.00
0.829	5.20	—	4.60	4.40	4.60	4.80
0.909	6.00	5.00	5.80	—	5.40	6.00

Thus stypticin is reduced at the dropping mercury electrode at pH values from 2.5 to 9 in the concentration range 0.117 to 0.909 millimoles/liter. In all cases only one polarographic wave was observed.

As the pH is increased there is a shift in reduction potential and the polarographic wave becomes less steep: from 0.8 to 1.0 V at pH 2.6 to 3.9 and from 0.9 to 1.3 V at pH 5.0 to 8.0. The slope of the polarographic wave on polarographic reduction of stypticin on a 2 N potassium chloride supporting electrolyte is even smaller (from 1.0 to 1.5 V).

SUMMARY

1. The conditions for the polarographic reduction of stypticin at different pH have been studied.

2. It has been established that with buffer solutions as supporting electrolytes reduction of stypticin takes place at the dropping mercury electrode at pH values from 2.5 to 9 in the potential range between 0.8 and 1.3 V (against the saturated calomel electrode) at concentrations between 0.117 and 0.909 millimoles/liter.

LITERATURE CITED

[1] A. P. Orekhov, The Chemistry of the Alkaloids (1955).

[2] A. M. Berkengeim, The Chemistry and Technology of Synthetic Medicinal Products (1935).

[3] N. A. Preobrazhensky and E. I. Genkin, The Chemistry of Organic Medicinal Materials (1953).

[4] Ya. Gelrovsky, Polarographic Methods (1937).

[5] I. M. Kolthoff and D. D. Lingane, Polarography (1948).

[6] H. F. W. Kirkpatrick, Quart. J. Pharmacy a. Pharmacology 18, Nos. 3 and 4 (1945); 19, Nos. 1-2 (1946).

[7] USSR Pharmacopeia, 8th ed. (1952).

Received November 3, 1955

Molotov Pharmaceutical Institute

THE DETERMINATION OF WATER IN COMPLEX COMPOUNDS USING THE FISCHER REAGENT

E. P. Zemlyakova

The use of the Fischer reagent (a solution of iodine, sulphur dioxide and pyridine in methyl alcohol) for the determination of water in liquids, solid compounds and gases has been described in the literature [1,2]. The aim of the present work was to study the possibility of determining the different functions of water in complex compounds using the Fischer reagent.

The following hydrated cobalt salts were synthesized for study:

$[Co(NH_3)_5H_2O]Cl_3$ (I)[3], $[Co(NH_3)_5H_2O]Br_3$ (II)[4],
$[Co(NH_3)_5H_2O](NO_3)_3$ (III)[5], $[Co(NH_3)_5H_2O]_2(SO_4)_3 \cdot 3H_2O$ (IV)[6],
$[Co(NH_3)_5H_2O]_2(C_2O_4)_3 \cdot 4H_2O$ (V)[7], $[Co(NH_3)_5H_2O]PO_4 \cdot 2H_2O$ (VI)[8].

The cobalt content in the salts obtained was first determined, after which the water was determined in parallel determinations by weighing and by titration with the Fischer reagent. By drying the crystalline hydrates in a drying oven at 110°, or in some cases (IV, VI) at 140-150°, the quantity of water in the compounds studied was obtained and found to differ very little from the theoretical calculated values (Table 1).

For the determination of water by the Fischer method, a sample of the material being studied was treated with an accurately measured quantity (20-25 ml) of anhydrous methyl alcohol and titrated with the Fischer reagent with gentle stirring until the yellow color of the solution obtained became brown. In a separate experiment, the water content in an equal volume (20-25 ml) of methyl alcohol was determined. Using this value, the water content in the crystalline hydrate being studied was calculated.

The experimental results (Table 1) show that in salts (I), (II), (III), whose vapour pressure at 25° is approximately 5-4 mm of mercury, the water cannot be determined by the Fischer reagent.

In the complex compounds (IV), (V), (VI) only part of the water can be determined: namely $3H_2O$ out of $5H_2O$, $4H_2O$ out of $6H_2O$ and $2H_2O$ out of $3H_2O$.

On titration of the salt

$$[Co(NH_3)_5H_2O]_2(Cr_2O_7)_3 \cdot 3H_2O$$

no definite results could be obtained. The Cr_2O_7 ion, which acts as an oxidizing agent, evidently interferes with the water determination by the Fischer reagent.

The determination of water in hydrated cobalt salts using the Fischer reagent has shown that in the crystalline hydrates only the water less firmly bound to the complex-forming atom can be determined.

The same results obtained after stirring a salt hydrate sample mechanically for 4 hours with 25 ml of anhydrous methyl alcohol. The only difference is that after the 4-hour mechanical stirring with methyl alcohol the material being studied (the salt hydrate) was titrated more rapidly and more distinctly; when the prolonged mechanical stirring is not carried out the titration takes place slowly and the end-point is less sharply defined.

TABLE 1

Compounds studied	Cobalt content (%)		Theoretical water content		Quantity of water, obtained by weighing				Quantity of water, obtained by the Fischer method		
	theoretical	obtained experimentally	%	in moles	temperature	%	in moles	deviation from theoretical (in moles)	%	in moles	deviation from theoretical (in moles)
$[Co(NH_3)_5H_2O]Cl_3$	21.96	22.1	6.78	1	110°	6.57	0.97	—0.03	—	—	—
$[Co(NH_3)_5H_2O]Br_3$	14.67	14.38	4.48	1	110	4.39	0.98	—0.02	—	—	—
$[Co(NH_3)_5H_2O](NO_3)_3$	16.94	17.28	5.16	1	110	5.02	0.97	—0.03	—	—	—
$[Co(NH_3)_5H_2O]_5(C_2O_2)_3 \cdot 4H_2O$	17.86	17.69	16.37	6	110	16.49	6.05	+0.05	11.70	4.27	—1.73
$[Co(NH_3)_5H_2O]_2(SO_4)_3 \cdot 3H_2O$	17.70	17.58	13.5	5	140—150	13.07	4.82	—0.18	8.79	3.24	—1.76
$[Co(NH_3)_5H_2O]PO_4 \cdot 2H_2O$	20.12	19.72	18.44	3	140—150	18.55	3.02	+0.02	12.69	2.06	—0.94

TABLE 2

Compounds studied	Theoretical water content		Quantity of water, obtained by weighing (at 100–110°)			Quantity of water, obtained by the Fischer method		
	%	in moles	%	in moles	deviation from theoretical (in moles)	%	in moles	deviation from theoretical (in moles)
$CuSO_4 \cdot 5H_2O$	36.10	5	35.88	4.98	—0.02	31.77	4.40	—0.6
$Na_2S_2O_3 \cdot 5H_2O$	36.30	5	36.01	4.83	—0.17	37.57	5.14	+0.14
$BaCl_2 \cdot 2H_2O$	14.75	2	14.67	2	0.00	14.74	2.00	0.00

As well as the hydrated cobalt salts studied, the water was determined in the crystalline zirconium hydrates:*

$$[Zr(C_2O_4)_2] \cdot xH_2O \quad (VII),$$
$$K_4[Zr(C_2O_4)_4] \cdot xH_2O \quad (VIII),$$
$$Ca_2[Zr(C_2O_4)_4] \cdot xH_2O \quad (IX).$$

Titration of these compounds with the Fischer reagent in anhydrous methyl alcohol, with gentle stirring during the titration, takes place gradually. The end-point was clearly defined. In the salt (VII) $2H_2O$ were determined, while after drying in a desiccator over calcium chloride for several days $1.5H_2O$ were found by titration. In the complex compound (VIII) $4H_2O$ were determined, and $5.65H_2O$ in (IX).

The results obtained agree with experimental analytical data for these crystalline zirconium hydrates.

The results of experiments on the determination of water in barium chloride show that the amount of water in $BaCl_2 \cdot 2H_2O$, determined by weighing and by the Fischer method is practically the same. The crystalline hydrate $BaCl_2 \cdot 2H_2O$ is titrated sharply and rapidly. In the determination of water in sodium thiosulfate some discrepancies are observed: higher results are obtained in the titration with the Fischer reagent. In the determination of water in copper sulfate by the Fischer reagent, lower results are obtained (Table 2).

SUMMARY

1. In the salts $[Co(NH_3)_5H_2O]Cl_3$, $[Co(NH_3)_5H_2O]Br_3$ and $[Co(NH_3)_5H_2O](NO_3)_3$ the water in the inner sphere of the complex compound cannot be determined by the Fischer reagent.

2. In the salts $[Co(NH_3)_5H_2O]_2(SO_4)_3 \cdot 3H_2O$, $[Co(NH_3)_5H_2O]_2(C_2O_4)_3 \cdot 4H_2O$, $[Co(NH_3)_5H_2O]PO_4 \cdot 2H_2O$ the water in the outer sphere may be determined by the Fischer reagent under the conditions studied; water which is more firmly bound to the complex-forming atom is not determined.

3. In the determination of water by the Fischer reagent it is necessary to bear in mind the complications which may arise on account of reaction between the compound being studied and the constituents of the Fischer reagent.

LITERATURE CITED

[1] K. Fischer, Z. ang. Chem. 48, 394 (1935).

[2] R. A. Lastovsky, Technical Analysis in the Manufacture of Dyes and Intermediate Products (1949), 18.

[3] Willand and Halle, J. Am. Chem. Soc. 44, 2220 (1922); L. K. Lenin, Inorganic Synthesis. (An Introduction to Preparative Inorganic Chemistry). 173 (1932).

[4] Inorganic Synthesis, coll. I. 181 (1951).

[5] S. M. Iorgensen, Z. anorg. Chem. 17, 461 (1898); I. C. Duff, J. Chem. Soc. 123, 565 (1923).

[6] Fremy, Ann. Chem. Phys., (3) 35, 298 (1852); Liebigs Ann. 83, 306 (1852).

[7] W. Gibbs and F. A. Genth, Am. J. Sci. (2), 23, 253 (1857).

[8] R. Klement, Z. allg. anorg. Chem. 156, 243 (1926); I. C. Duff, J. Chem. Soc. 123, 568 (1923).

Received November 21, 1955

The Lenin Soviet Technological
Institute, Leningrad

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* Prepared by V. I. Astapovich.

THE FUSIBILITY, VISCOSITY AND DENSITY OF THE SYSTEMS $SnBr_4-CH_2BrCOOH$ and $SbBr_3-CH_2BrCOOH$

T. Sumarokova and N. Khakhlova

Physico-chemical analysis of the systems $SbCl_3-CH_3COOH$ [1], $SbCl_3-CH_2ClCOOH$ [2] and $SbCl_3-CCl_3-COOH$ [3] has shown that acetic and chloroacetic acids undergo an acid-base reaction with antimony trichloride with the formation of complex compounds of composition $SbCl_3 \cdot RCOOH$ and $2SbCl_3 \cdot RCOOH$. Acetic [4, 5] and monochloroacetic [6] acids react with stannic chloride. Dichloroacetic and trichloroacetic acids [7] do not react with stannic chloride. M. Usanovich and E. Yakovleva [8] have studied the behaviour of CH_3COOH towards $SnBr_4$ and have established that the $SnBr_4$ reacts with CH_3COOH.

In connection with these experiments it appeared of interest to us to study the behaviour of $CH_2BrCOOH$ towards $SnBr_4$ and $SbBr_3$. It is known that $CH_2BrCOOH$ behaves in water as a stronger acid ($K = 2.05 \cdot 10^{-3}$ at 25°) than $CH_2ClCOOH$ ($K = 1.40 \cdot 10^{-3}$ at 25°) and consequently ought to be a weaker oxonium base than $CH_2ClCOOH$. On the other hand, $SnBr_4$ has less complex-forming power than $SnCl_4$. $SbBr_3$ on the contrary forms complex compounds more readily than $SbCl_3$, so that interaction might be expected in the $SbBr_3-CH_2BrCOOH$ system but not in the $SnBr_4-CH_2BrCOOH$.

EXPERIMENTAL

Antimony tribromide was synthesized by the direct action of bromine on metallic antimony. The crude product obtained, containing excess bromine, was boiled over metallic antimony for several hours and then redistilled. In the final purification the antimony tribromide was sublimed and stored in sealed ampoules; m. p. 93°.

Stannic bromide was prepared similarly to the antimony tribromide. Purification of the stannic bromide was achieved by fractional distillation. The fraction boiling at 199° and 695 mm pressure was collected and sealed into ampoules in a special apparatus [9]. The stannic bromide had m. p. 32°.

Monobromoacetic acid was obtained by bromination of glacial acetic acid, of m.p. 16°, in the presence of red phosphorus. The acetic acid was fully brominated and the product crystallized completely at room temperature. The monobromoacetic acid obtained was redistilled several times, recrystallized twice from benzene, distilled into ampoules and sealed. The monobromoacetic acid had m. p. 49.8°.

The system $SnBr_4-CH_2BrCOOH$ was studied, measurements being made of the fusibility and the viscosity and density at 40, 50, 60 and 70°. From Figure 1 and the data in Table 1 it can be seen that the fusion diagram has the form of a simple eutectic. The eutectic point corresponds to a temperature of 28.8° and a composition of 87.27 mole % $SnBr_4$. In the melts of some mixtures, crystallization was preceded by the appearance of a slight turbidity, apparently connected with the separation of the system into its components.

Neither the system $SnBr_4-CH_2BrCOOH$ nor its components conducts electricity.

The viscosity isothermal (Table 2, Figure 1) passes through a minimum corresponding to a composition of 85-90 mole % $SnBr_4$. With increasing temperature the position of the minimum shifts towards the monobromoacetic acid side. The minimum on the viscosity isothermals results from the association of the monobromoacetic acid.

The density data are given in Table 3.

TABLE 1

Fusibility of the System $SnBr_4-CH_2BrCOOH$

$SnBr_4$ content (mole %)	Temperature of initial crystallization	Temperature of eutectic crystallization
100.00	32.0°	–
90.42	29.5	28.3°
87.27	28.8	28.8
74.50	35.0	28.5
73.48	34.7	28.5
50.00	40.2	28.0
44.40	41.0	28.5
35.00	41.8	27.7
23.79	43.7	28.5
21.00	43.8	28.7
9.20	45.6	–
8.17	46.0	–
0.00	49.8	–

TABLE 2

Viscosity of the System $SnBr_4-CH_2BrCOOH$

$SnBr_4$ content (mole %)	Viscosity (in centipoises)			
	40°	50°	60°	70°
100.00	1.97	1.78	1.58	1.42
90.42	1.88	1.65	1.47	1.32
72.68	2.04	1.78	1.56	1.38
47.94	2.48	2.15	1.81	1.59
26.36	3.07	2.58	2.15	1.82
8.95	3.74	3.12	2.58	2.13
0.00	–	3.65	3.03	2.52

The relationship between specific volume and composition (in % wt.) (Figure 1) is linear and indicates that the components of the system do not interact.

Thus the absence of electrical conductivity in the system and the shape of the viscosity and specific volume isothermals, together with the thermal analysis data, show that no interaction takes place between the components of the system.

The system $SbBr_3-CH_2BrCOOH$ was studied, measurements being made of the fusibility and the viscosity and density at 60, 70 and 80°. The thermal analysis data are given in Table 4.

The fusion diagram of the system $SbBr_3-CH_2BrCOOH$ (Figure 2) has one eutectic point at a composition of 10 mole% $SbBr_3$; the m. p. of the eutectic is 41°.

The results of measurements of viscosity and density are given in Tables 5 and 6.

TABLE 3

Density of the System $SnBr_4-CH_2BrCOOH$

$SnBr_4$ content		Density (g/ml)			
% wt.	mole %	40°	50°	60°	70°
100.00	100.00	3.3132	3.2894	3.2613	3.2287
96.74	90.42	3.2464	3.2199	3.1934	3.1594
89.35	72.68	3.0939	3.0701	3.0438	3.0116
74.84	47.94	2.8162	2.8005	2.7770	2.75[illegible]6
53.03	26.36	2.4955	2.4812	2.4626	2.4407
23.68	8.95	2.1538	2.1394	2.1216	2.1010
0.00	0.00	—	1.9268	1.9103	1.8891

A complete isothermal could be obtained only at 80°; at 60 and 70° mixtures enriched in antimony tribromide crystallized. The viscosity isothermal (Figure 2) at 80° has the form of an S-shaped curve and its path shows the occurrence of interaction in the system. The relationship between specific volume and composition expressed as percentage weight shows that a contraction is taking place in the system as a result of interaction (Figure 2).

On the basis of the results of viscosity and density measurements we conclude that the components of the system undergo an interaction which is not reflected in the fusion diagram.

TABLE 4

Fusibility of the System $SbBr_3-CH_2BrCOOH$

$SbBr_3$ content (mole %)	Temperature of initial crystallization	Temperature of eutectic crystallization
100.00	93.0°	–
74.93	86.0	38.5°
49.73	72.0	41.0
35.19	65.0	41.0
10.00	41.0	41.0
7.12	46.0	–
5.52	47.0	–
4.22	47.8	–
1.84	49.3	41.0
0.00	50.0	–

TABLE 5

Viscosity of the System $SbBr_3-CH_2BrCOOH$

$SbBr_3$ content (mole %)	Viscosity (in centipoises)		
	60°	70°	80°
100.00	–	–	4.94
80.08	–	–	4.56
70.77	–	–	4.38
59.77	–	–	4.17
49.64	6.06	4.71	3.83
40.63	5.34	4.26	3.44
27.40	4.51	3.56	2.96
15.26	3.79	3.11	2.58
12.86	3.66	3.00	2.51
2.31	3.19	2.65	2.25
0.00	3.15	2.63	2.22

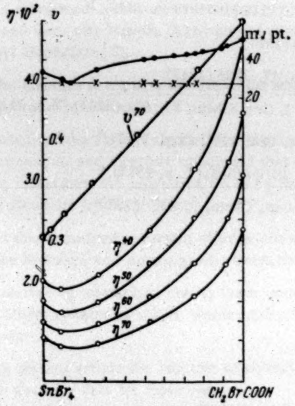

Fig. 1. Fusibility, viscosity and specific volume of the system $SnBr_4-CH_2BrCOOH$.

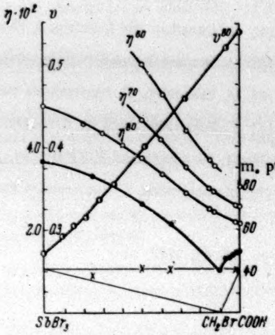

Fig. 2. Fusibility, viscosity and specific volume of the system $SbBr_3-CH_2BrCOOH$.

TABLE 6

Density of the System $SbBr_3-CH_2BrCOOH$

$SbBr_3$ content		Density (g /ml)		
% wt.	mole %	60°	70°	80°
100.00	100.00	—	—	3.7437
91.27	80.08	—	—	3.4520
86.30	70.77	—	—	3.3078
78.32	59.77	—	—	3.2036
71.96	49.64	3.0102	2.9860	2.9781
64.04	40.63	2.8029	2.7738	2.7562
49.57	27.40	2.5188	2.5023	2.4793
31.91	15.26	2.5779	2.2403	2.2217
27.72	12.86	2.2056	2.1900	2.1733
5.81	2.31	1.9628	1.9399	1.9235
0.00	0.00	1.9103	1.8891	1.8696

Thus the results of physicochemical analysis of the $SbBr_3-CH_2BrCOOH$ and $SnBr_4-CH_2BrCOOH$ systems has shown, as we suggested, that $CH_2BrCOOH$ reacts with $SbBr_3$ but does not react with $SnBr_4$.

SUMMARY

1. The fusibility and the viscosity and density at 40, 50, 60 and 70° of the system $SnBr_4-CH_2BrCOOH$ have been studied.

It has been established that there is no reaction between the components.

2. The fusibility and the viscosity and density (at 60, 70 and 80°) of the system $SbBr_3-CH_2BrCOOH$ have been studied.

It has been established from the viscosity and specific volume diagrams that reaction takes place.

LITERATURE CITED

[1] M. Usanovich and T. Sumarokova, J. Gen. Chem. 21, 989 (1951) (T.p. 1123).*

[2] M. Usanovich and T. Sumarokova, J. Gen. Chem. 21, 1214 (1951) (T.p. 1371).*

[3] T. Sumarokova and M. Usanovich, J. Gen. Chem. 21, 1219 (1951) (T.p. 1379).*

[4] J. Stranathan and J. Strong, J. Phys. Chem. 31, 1420 (1927).

[5] M. Usanovich and E. Kalabanovskaya, J. Gen. Chem. 17, 1235 (1947).

[6] M. Usanovich, T. Sumarokova and V. Glushchenko, J. Gen. Chem. 21, 981 (1951) (T.p. 1113).*

[7] T. Sumarokova and M. Usanovich, J. Gen. Chem. 21, 984 (1951) (T.p. 1117).*

[8] M. Usanovich and E. Yakovleva, J. Gen. Chem. 25, 1312 (1955) (T. p. 1257).*

[9] M. Usanovich, T. Sumarokova and V. Udovenko, J. Gen. Chem. 9, 1967 (1939).

Received July 11, 1955

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* T. p = C. B. Translation pagination.

THE VISCOSITY OF BINARY SYSTEMS WITH CHLORAL. I

V. V. Udovenko and R. I. Khomenko

It is known that the reaction of chloral with aliphatic alcohols leads in the majority of cases to the formation of crystalline compounds which have the structure of hemiacetals and are called chloral alcoholates. As Leopold [1], after a study of the fusion diagram of the chloral – ethyl alcohol system, has shown, the crystalline chloral alcoholates obtained in his case did not dissociate into their components on melting and are therefore fairly stable compounds. In some cases, however, the chloral alcoholates formed do not crystallize under ordinary conditions and form oily liquids. Examples of such chloral alcoholates are chloral propyl alcoholate [2] and chloral amyl alcoholate [3].

Cyclic alcohols react with chloral in the same way as aliphatic alcohols, forming corresponding crystalline or liquid chloral alcoholates [4].

In a study of the chloral alcoholates, Jacobsen [5] tried to obtain chloral alcoholates of aromatic alcohols. He was unsuccessful, and therefore concluded that chloral does not react with aromatic alcohols. This conclusion by Jacobsen contradicts the suggestion made by Henry [6] that chloral can be used as a reagent for compounds containing the alcoholic hydroxyl group.

It has thus remained uncertain whether chloral reacts with all hydroxyl-containing materials and how the nature of the hydroxyl-containing group affects the character of its reaction with chloral.

In undertaking research to clarify these questions, we decided to study by physicochemical analytical methods a series of binary systems in which, besides chloral, materials belonging to different classes of organic compounds would be taken.

In the present article the reaction of chloral with benzyl alcohol and with cyclohexanol is examined on the basis of the viscosity data for these systems.

Determination of the viscosity was carried out in a viscometer adapted for volatile liquids [7]. The mixture being measured was carefully isolated from the atmosphere to avoid entry of moisture. The density was measured in a pyknometer of 1 ml capacity with a narrow graduated neck. The temperature in the thermostat was regulated within ±0.05°.

The chloral required was prepared from chloral hydrate by Liebig's method [8], in which concentrated sulfuric acid is used as dehydrating agent. The chloral obtained was distilled from freshly ignited calcium oxide in a special apparatus [7]. The benzyl alcohol was dried over ignited potassium carbonate and afterwards distilled, while the cyclohexanol was first of all frozen and afterwards the fraction with melting point above 20° was distilled. Materials used had the following boiling points at 726 mm: chloral 96.7°, benzyl alcohol 202.5° and cyclohexanol 158.8°.

When the chloral and benzyl alcohol were mixed a considerable evolution of heat was observed, so that the mixtures were cooled during preparation. The viscosity of the prepared mixtures for this system did not change with time. Measurements were made at 25, 50 and 75°.

The results of the viscosity and density measurements for the chloral – benzyl alcohol system are given in Table 1. The viscosity isothermals have the form of curves with a sharply defined maximum, which does not correspond to a rational component ratio. On increasing the temperature the maximum becomes flatter and is displaced to the alcohol side. The density isothermals are curves concave towards the composition axis.

TABLE 1

The Chloral - Benzyl Alcohol System

Chloral content (in moles %)	25°		50°		75°	
	Viscosity	Density	Viscosity	Density	Viscosity	Density
0.00	5.212	1.0190	2.548	1.0006	1.501	0.9819
9.86	7.956	1.1071	3.521	1.0862	1.934	1.0661
18.91	12.34	1.1674	4.774	1.1454	2.422	1.1225
27.95	18.57	1.2312	6.410	1.2083	2.948	1.1829
35.62	21.83	1.2843	6.783	1.2592	3.175	1.2339
40.64	40.42	1.3215	9.558	1.2944	3.772	1.2650
43.64	50.35	1.3424	10.85	1.3142	4.165	1.2837
47.51	55.16	1.3678	10.57	1.3352	3.888	1.3053
49.30	54.24	1.3780	10.21	1.3460	3.873	1.3118
49.98	51.18	1.3817	10.01	1.3510	3.779	1.3170
53.95	39.89	1.3942	8.491	1.3632	3.258	1.3288
59.25	24.53	1.4194	6.780	1.3887	2.953	1.3531
66.79	9.262	1.4387	3.796	1.4075	2.066	1.3732
75.64	2.888	1.4600	1.639	1.4233	1.115	1.3909
88.27	2.072	1.4906	1.307	1.4557	0.922	1.4123
100.00	1.055	1.5013	0.764	1.4603	0.588	1.4186

TABLE 2

The Chloral – Cyclohexanol System

Cloral content (in moles %)	60°		80°	
	viscosity	density	viscosity	density
0.00	8.254	0.9187	3.721	0.9019
12.19	9.350	1.0019	4.145	0.9831
19.98	10.065	1.0544	4.409	1.0334
24.91	10.440	1.0900	4.547	1.0700
29.84	10.492	1.1234	4.576	1.1014
34.99	10.495	1.1633	4.587	1.1397
39.76	10.199	1.1925	4.493	1.1688
44.85	9.316	1.2317	4.178	1.2065
49.60	7.757	1.2647	3.602	1.2388
59.51	3.994	1.3098	2.388	1.2830
70.22	2.054	1.3456	1.432	1.3181
79.73	1.327	1.3778	1.008	1.3511
89.17	0.931	1.4076	0.743	1.3794
100.00	0.701	1.4413	0.565	1.4096

On mixing chloral and cyclohexanol a large evolution of heat was also observed, so that the mixtures were cooled during preparation. Crystals melting at 60° were precipitated from the mixture of chloral and cyclohexanol. All viscosity and density measurements were therefore made at 60 and 80°. The viscosity of the mixtures did not change with time.

The results of the viscosity and density measurements for the chloral – cyclohexanol system are given in Table 2. The viscosity isothermals pass through an irrational maximum which corresponds to a chloral mole % of 90. On raising the temperature the viscosity maximum becomes flatter and in the temperature range studied moves only very slightly toward the alcohol side. The density isothermals are concave towards the composition axis.

A mixture of equimolecular amounts of chloral and cyclohexanol crystallized completely. On recrystallization from petroleum ether the crystals had m. p. 64°. They dissolved readily in alcohol, acetone, benzene and less readily in petroleum ether. Determination of chlorine by the Carius method gave the following results:

Found %: Cl 43.13, 43.18. $CCl_3CHO \cdot C_6H_{11}OH$. Calculated %: Cl 42.97.

The analysis and melting point correspond to the compound of chloral and cyclohexanol $CCl_3CHO \cdot C_6H_{11}OH$, described by Sumerford and Cronic [4].

As is known, the chloral alcoholates formed by the interaction of chloral and aliphatic alcohols are stable compounds which do not dissociate into their components on melting [1]. Study of the viscosity of such systems [8 – 11] has also shown that the isothermals are not single but pass through an irrational maximum corresponding closely to the composition of the equimolecular compound but displaced to the alcohol side. This displacement of the irrational maximum on the viscosity isothermals, as is well known [12], is explained by the reaction of the compound formed with one of the components of the system.

In the chloral – benzyl alcohol system studied by us the viscosity isothermals pass through a sharply defined irrational maximum similarly situated near the composition of the equimolecular compound but displaced to the alcohol side.

The similar character of the viscosity isothermal indicates interaction between chloral and benzyl alcohol and the formation of an equimolecular compound. The reaction of this compound with the alcohol leads to a displacement of the maximum toward the side of the latter.

On the basis of our experimental data, Jacobsen's statement that chloral does not react with aromatic alcohols must be considered incorrect [5].

In spite of the clearly defined reaction between chloral and benzyl alcohol, however, we were unable to separate the compound in crystalline form. On distilling an equimolecular mixture the high-boiling fraction proved to be pure benzyl alcohol. The compound formed therefore decomposes into its components at the boiling point.

In the chloral – cyclohexanol system the reaction of the components leads to the formation of a crystalline compound. At the same time the maximum on the viscosity isothermals of this system is less sharply defined than in the chloral – benzyl alcohol system and corresponds to a cyclohexanol mole % of 70. This corresponds to a component ratio of 1 : 2 in the compound.

Assuming that the crystalline compounds of chloral and cyclic alcohols are as stable as those of aliphatic alcohols and are not noticeably dissociated into their components at the melting points, it may be concluded that such a shift of the viscosity maximum to the cyclohexanol side is explained by the reaction of the latter with the equimolecular compound. This conclusion fully agrees with the conclusion reached by one of us in an examination of the reasons for the shift of the irrational maximum on viscosity isothermals [12, 11].

SUMMARY

[1] The viscosity and density of the chloral – benzyl alcohol system at 25, 50 and 70°, and of the chloral – cyclohexanol system at 60 and 80° have been studied.

[2] From the example of the chloral – benzyl alcohol system it has been shown that aromatic alcohols react with chloral in the same way as aliphatic alcohols.

[3] It has been shown that in the systems studied the shift of the irrational maximum to the alcohol side is caused by the reaction of the latter with the equimolecular compound.

LITERATURE CITED

[1] G. H. Leopold, Z phys. Chem. 66, 359 (1909).

[2] E. Gabuti, Gazz. 31, I, 86 (1901).

[3] Beilst I, 622.

[4] W. T. Sumerford and F. M. Cronic, J. Am. Chem. Soc. 70, 448 (1948).

[5] O. Jacobsen, Liebigs Ann. 157, 234 (1871).

[6] L. Henry, Ber. 7, 762 (1874).

[7] M. I. Usanovich, T. N. Sumarokova and V. V. Udovenko, J. Gen. Chem. 9, 1967 (1939).

[8] N. S. Kurnakov and N. N. Efremov, J. Russ. Phys.-Chem. Soc. 45, 329 (1913).

[9] N. K. Efremov, Bull. Inst. Phys.-Chem. Analysis 4, 118 (1928).

[10] N. N. Efremov, Bull. Inst. Phys.-Chem. Analysis 1, 61 (1949).

[11] V. V. Udovenko, E. I. Kalabanovskaya and M. F. Prokopyeva, J. Gen. Chem. 19, 165 (1949).

[12] V. V. Udovenko, The Viscosity of Liquids and Colloidal Solutions, II. (Acad. Sci. USSR Press, 1944), 89.

Received November 12, 1955

Mid-Asia State University and Kiev
Polytechnical Institute

SPECTRA AND HALOCHROMISM

I. HALOCHROMISM OF AROMATIC CARBINOLS

V. F. Lavrushin

The production of color from the interaction of triphenylcarbinol and concentrated sulfuric acid had been called halochromism [1]. This phenomenon has been studied by many methods for a large number of aromatic carbinols. The absorption spectra have been studied chiefly with solutions of tertiary aromatic alcohols in concentrated sulfuric acid.

In the present work our aim was the spectrographic study of the behavior of carbinols with varying numbers of aromatic radicals, dissolved in concentrated sulfuric acid, trichloroacetic acid and a mixture of sulfuric and acetic acids.

The General Characteristics of the Absorption Spectra Studied

Triphenylcarbinol dissolves fairly rapidly in concentrated sulfuric acid and an orange color is developed immediately. The absorption spectrum of the sulfuric acid solution lies between 4850 and 2150 A and has 4 absorption bands (I-IV) (Figure 1, Curve 2).

I		II		III		IV	
λ	ϵ	λ	ϵ	λ	ϵ	λ	ϵ
4200	50000	2900	3100	2620	4000	2280	16000

Band I, which gives rise to the color of the solution, and Band II are characteristic only of the acid solution and are not present in the curve of the ethyl alcohol solution. This absorption curve agrees exactly with curves given in the literature [2,3] and supplements them in the far ultra-violet region.

Triphenylcarbinol also forms an immediate orange color on solution in 30% sulfuric acid in glacial acetic. The absorption curve of this solution has one broad band between 5000 and 3200 A with a slight depression giving it two maxima at 4250 and 3860 A and ϵ = 31600 (Figure 1, Curve 4).

The solution of triphenylcarbinol in 90% trichloroacetic acid gives a curve with one absorption band between 5060 and 3200 A, which has one maximum at 4330 A and ϵ = 79400 (Figure 1, Curve 3).

4-Hydroxytriphenylcarbinol dissolves in concentrated sulfuric acid to form a colored solution whose curve has four absorption Bands (I-IV) (Figure 1, Curve 5).

I		II		III		IV	
λ	ε	λ	ε	λ	ε	λ	ε
4580	63000	3900	20000	2900	1740	2500	10700

The first two bands cover a large part of the visible and ultraviolet spectrum and are given only by the acid solution.

These bands are situated in the same region of the spectrum for the acetic – sulfuric acid solution curve, but are of lower intensity (Figure 1, Curve 6). They have two absorption maxima, the first of which lies at 4650 A and ϵ = 31600 and the second at 3750 A and ϵ = 9550.

Diphenylcarbinol dissolves in concentrated sulfuric acid to form an orange solution whose absorption curve lies between 5400 and 2170 A and has three well-defined absorption Bands (I-III) (Figure 2, Curve 2).

I		II		III	
λ	ε	λ	ε	λ	ε
4430	20400	2840	3170	2280	30150

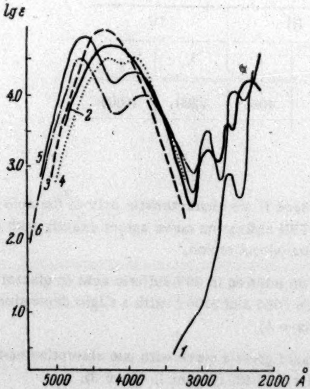


Fig. 1. Triphenylcarbinol: 1) in C_2H_5OH, 2) in conc. H_2SO_4, 3) in 90% CCl_3COOH, 4) in 30% H_2SO_4 in CH_3COOH.

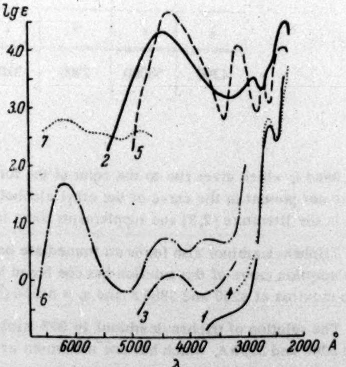


Fig. 2. Diphenylcarbinol: 1) in C_2H_5OH, 2) in conc. H_2SO_4, 3) in 90% CCl_3COOH. Methyldiphenylcarbinol: 4) in C_2H_5OH, 5) in conc. H_2SO_4, 6) in 90% CCl_3COOH, 7) in 55% H_2SO_4 in CH_3COOH.

The curve obtained by us for the sulfuric acid solution of diphenylcarbinol agrees with that given in the literature [4].

Diphenylcarbinol dissolves readily in 90% trichloroacetic acid again forming a colored solution. The absorption curve of this solution has only one band of low intensity with an absorption maximum at 4280 A and ϵ = 1.25 (Figure 2, Curve 3).

Methyldiphenylcarbinol dissolves in concentrated sulfuric acid to form an orange-colored solution which has a characteristic spectrum with four well-defined absorption Bands (I-IV) (Figure 2, Curve 5).

I		II		III		IV	
λ	ε	λ	ε	λ	ε	λ	ε
4340	47000	3110	11800	2680	2140	2310	10000

Both long wave bands are given only by the sulfuric acid solution and are not present in the ethanol curve. This curve does not differ in any way from that given in the literature [4].

When methyldiphenylcarbinol is dissolved in 90% trichloroacetic acid a yellow color is formed for only a short time, changing rapidly to blue-green. The absorption curve of this solution shows three bands between 6700 and 3300 A (Figure 2, Curve 6). On comparison with the sulfuric acid solution curve a large new long wave band with a maximum at 6150 A and ϵ = 50 is observed, after which comes a band in the short wave region of the visible spectrum with a maximum at 4420 A and ϵ = 5.0 and one in the near ultraviolet at 3670 A and ϵ = = 5.0.

Methyldiphenylcarbinol also dissolves in 55% sulfuric acid in glacial acetic with the formation of a blue-green color. The absorption curve of this solution lies between 6420 and 4500 A (Figure 2, Curve 7) and has two absorption maxima at 6170 A and ϵ = 1180 and at 4700 A and ϵ = 654.

In 55% sulfuric acid solution in acetic anhydride, methyldiphenylcarbinol does not give a blue-green color but forms an orange solution as with sulfuric acid.

Since methyldiphenylcarbinol forms solutions with noticeably different colors in different acids, it seemed of interest to study the behavior of carbinols of closely related structure in analogous conditions.

Ethyldiphenylcarbinol gives an orange solution with concentrated sulfuric acid. The absorption curve of the solution has four absorption Bands (I-IV) (Figure 3, Curve 2).

I		II		III		IV	
λ	ε	λ	ε	λ	ε	λ	ε
4250	20000	3150	10000	2700	2000	2350	10000

This curve is of the same shape as the curve of the corresponding methyldiphenylcarbinol solution.

On testing the behavior of ethyldiphenylcarbinol in trichloroacetic acid and 55% sulfuric acid in acetic an orange color was obtained which did not change to blue-green even after a time interval.

Methyldiphenylenecarbinol is sparingly soluble in concentrated sulfuric acid. The light brown solution obtained gives an absorption curve with a well-defined band in the visible region of the spectrum at 4950 A and ϵ = 200. A band with maximum at 2820 A and ϵ = 20000 lies in the ultraviolet region of the spectrum. There

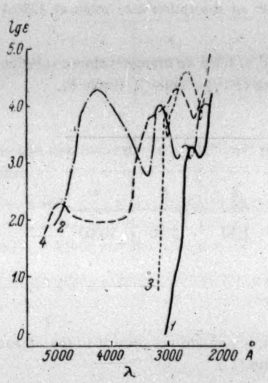


Fig. 3. Ethyldiphenylcarbinol: 1) in C_2H_5OH, 2) in conc. H_2SO_4. Methyldiphenylenecarbinol: 3) in C_2H_5OH, 4) in conc. H_2SO_4.

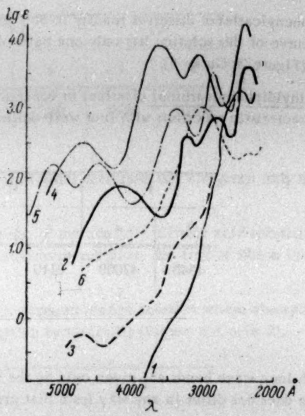


Fig. 4. Dimethylphenylcarbinol: 1) in C_2H_5OH, 2) in conc. H_2SO_4, 3) in 90% CCl_3COOH. Dimethylanisylcarbinol: 4) in conc. H_2SO_4, 5) in 30% H_2SO_4 in CH_3COOH.

is a marked inflection in the long-wave region of this curve (Figure 3, Curve 4). The ultraviolet region of the curve as a whole resembles the curve of the ethanol solution.

Methyldiphenylenecarbinol did not give a blue-green coloration in trichloroacetic acid or in 55% sulfuric acid in glacial acetic.

Dimethylphenylcarbinol in concentrated sulfuric acid solution gives an orange-red color and shows a bright light-green fluorescence under ultraviolet light. Selective absorption is shown in the absorption spectrum of this solution by four Bands (I-IV) (Figure 4, Curve 2).

I		II		III		IV	
λ	ε	λ	ε	λ	ε	λ	ε
4130	80	3200	400	2800	800	2300	4700

The curve for the solution of this carbinol in trichloroacetic acid (Figure 4, Curve 3) differs in appearance from that of the sulfuric acid solution. It has only one absorption band with a maximum at 4920 A and $\epsilon = 0.6$. The remaining part of the curve approaches the absorption curve of the ethanol solution after two inflections.

Dimethyl-p-anisylcarbinol gives a red solution in concentrated sulfuric acid [5]. Its absorption spectrum is characterized by a curve with four absorption Bands (I-IV) (Figure 4, Curve 4).

I		II		III		IV	
λ	ε	λ	ε	λ	ε	λ	ε
4680	316	3596	8100	3000	6200	2310	10700

In the absorption curve of dimethyl-p-anisylcarbinol in 30% sulfuric acid in acetic (Figure 4, Curve 5) a splitting of the long wave band into two parts with maxima at 5100 and 4450 A and ε = 160 takes place. Two other bands are displaced towards the short wave region and have maxima at 3340 A and ε = 1000 and at 2800 A and ε = 3300. The band of shortest wavelength is missing from this curve as a result of the absorption by acetic acid in this region of the spectrum.

DISCUSSION OF RESULTS

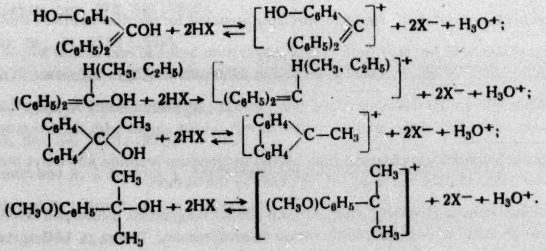
Our spectrographic study of the behavior of aromatic carbinols in strong acids shows that all of them, although colorless compounds, give colored solutions by interaction with the acids. The absorption curves of such solutions in the medium and short-wave ultraviolet show as a rule the selective absorption characteristic of the ethanol solutions. In the visible region of the spectrum and at its border new bands appear which are present only in the acid solutions and which disappear on dilution with water or with organic solvents. This property is typical of materials which are capable of showing halochromism.

As is known, the phenomenon of halochromism of triphenylcarbinol has been well studied [6] and involves the acid-base reaction:

$$(C_6H_5)_3COH + 2H_2SO_4 \rightleftarrows [(C_6H_5)_3C]^+ + 2HSO_4^- + H_3O^+.$$

The formation of the carbonium ion is the cause of the appearance of the color, so that its removal as a result of hydrolysis or solvolysis of the carbonium salt leads to decolorization of the solution. The existence of carbonium ions has been confirmed in many studies by electrolysis, conductivity measurements, cryoscopy, absorption spectra measurement and by chemical methods.*

Since all the carbinols studied behave in analogous fashion irrespective of the number of aromatic radicals present in their molecules it may be assumed that they all undergo a similar acid-base reaction with the formation of the corresponding carbonium salts, whose cations are responsible for the color of the solutions:



$$\begin{matrix}HO{-}C_6H_4 \\ (C_6H_5)_2\end{matrix}\!>\!COH + 2HX \rightleftarrows \left[\begin{matrix}HO{-}C_6H_4 \\ (C_6H_5)_2\end{matrix}\!>\!C\right]^+ + 2X^- + H_3O^+;$$

$$(C_6H_5)_2{=}\overset{H(CH_3,\ C_2H_5)}{\overset{|}{C}}{-}OH + 2HX \rightarrow \left[(C_6H_5)_2{=}\overset{H(CH_3,\ C_2H_5)}{\overset{|}{C}}\right]^+ + 2X^- + H_3O^+;$$

$$\begin{matrix}C_6H_4 \\ | \\ C_6H_4\end{matrix}\!>\!C\!<\!\begin{matrix}CH_3 \\ OH\end{matrix} + 2HX \rightleftarrows \left[\begin{matrix}C_6H_4 \\ | \\ C_6H_4\end{matrix}\!>\!C{-}CH_3\right]^+ + 2X^- + H_3O^+;$$

$$(CH_3O)C_6H_5{-}\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}{-}OH + 2HX \rightleftarrows \left[(CH_3O)C_6H_5{-}\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}\right]^+ + 2X^- + H_3O^+.$$

---

* See especially [6-17].

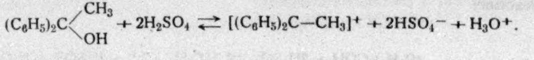
The absorption curves of the different types of carbonium ion are so characteristic that the ions can apparently be identified by their absorption spectra.

The behavior of methyldiphenylcarbinol was unexpected in that it gave a blue-green solution in trichloroacetic acid, in contrast to the orange color of the sulfuric acid solution, and, which is particularly interesting, gave the same color in a sulfuric acid solution in glacial acetic. As we have seen earlier, additional long-wave bands are present in the absorption curves of these solutions. The nearest homolog, ethyldiphenylcarbinol, does not show this property.

An attempt to find some difference in the behavior of the differently colored solutions of methyl- and ethyldiphenylcarbinol in trichloroacetic acid using cryoscopic methods was unsuccessful, since the coefficient i for both compounds changed in identical fashion with time and reached a value of the order of 7.

Time (in hours)	Methyldiphenylcarbinol (M=198)		Ethyldiphenylcarbinol (M=212)	
	apparent molecular weight	i	apparent molecular weight	i
0.5	79.2	2.5	76.1	2.8
2	58.2	3.4	66.4	3.2
24	48.1	4.1	48.8	4.2
48	28.9	6.9	33.1	6.4
72	26.1	7.6	29.1	7.2

In the determination of i for methyldiphenylcarbinol in sulfuric acid the value 4 was obtained [18], which agrees well with acid-base reaction:



$$(C_6H_5)_2C\begin{matrix}\diagup CH_3\\ \diagdown OH\end{matrix} + 2H_2SO_4 \rightleftarrows [(C_6H_5)_2C{-}CH_3]^+ + 2HSO_4^- + H_3O^+.$$

For diphenylcarbinol in analogous conditions, however, this value also changed with time and rose to 6 [16]. It is possible that in trichloroacetic acid further processes involving the formation of carbonium ions take place in addition to the acid-base reaction.

Thus the problem of the anomalous halochromism of methyldiphenylcarbinol remains obscure and requires further study.

Synthesis and Purification of Specimens

The triphenylcarbinol was synthesized from phenyl magnesium bromide and ethyl benzoate [19]. For the spectrographic work the product was recrystallized repeatedly from ethyl alcohol. The triphenylcarbinol obtained melted at 162°, which agrees with the literature data [20].

The 4-hydroxytriphenylcarbinol* used was specially prepared for physicochemical studies.

The diphenylcarbinol was prepared from phenyl magnesium bromide and benzaldehyde [21]. On recrystallization from a small volume of ethyl alcohol it melted at 69°, confirmed by literature data [22].

The methyldiphenylcarbinol was synthesized from phenyl magnesium bromide and ethyl acetate [23]. After recrystallization from ethyl alcohol the product melted at 83°, which agrees with the literature data [24].

The ethyldiphenylcarbinol was obtained from phenyl magnesium bromide and ethyl propionate [25]. The product recrystallized from alcohol had m.p. 95°, as given by the authors.

The methyldiphenylenecarbinol was obtained from phenyl magnesium iodide and fluorenone [26]. A pure colorless product was obtained by recrystallization from dichloroethane. The m.p. 174° agreed with the data given in the method.

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* The specimen was kindly made available by I. S. Ioffe to whom we are extremely grateful.

The dimethylphenylcarbinol was synthesized from phenyl magnesium bromide and acetone [27]. The product was redistilled repeatedly in vacuo from a flask with a fractionating column 15 cm in length. Part of the fraction distilling at 90° and 10 mm was taken for study in accordance with the data given in the method.

The dimethylanisylcarbinol was prepared from anisyl magnesium bromide and acetone [5, p. 1082]. It was purified by vacuum distillation in the same way as dimethylphenylcarbinol. The product was collected at 105° and 5 mm.

The absorption spectra were measured using a photographic method [28, 29].

In conclusion we have to express our gratitude to A. N. Terenin for interest shown and valuable advice given.

SUMMARY

1. A spectrographic study has been made of the behavior of triphenylcarbinol, 4-hyroxytriphenylcarbinol, diphenylcarbinol, methyl- and ethyldiphenylcarbinol, methyldiphenylenecarbinol, dimethylphenylcarbinol and dimethylanisylcarbinol in concentrated sulfuric acid, 90% trichloroacetic acid and a solution of sulfuric acid in glacial acetic.

2. All the carbinols studied are capable of showing halochromism irrespective of the number of aromatic radicals in their molecules.

3. From the absorption spectra and the behavior of the acid solutions it is concluded that the cause of color production is the formation of carbonium ions.

4. Anomalous behavior has been observed in the halochromism of methyldiphenylcarbinol.

LITERATURE CITED

[1] A. Bayer and V. Villiger, Ber. 35, 1189 (1902).

[2] L. C. Anderson, J. Am. Chem. Soc. 52, 4567 (1930).

[3] C. S. Schoepfle and J. D. Rian, J. Am. Chem. Soc. 54, 3687 (1932).

[4] V. Gold and F. L. Tye, J. Chem. Soc. 1952, 2172.

[5] S. Skraup and F. Freundlich, Ber. 55, 1073 (1922).

[6] L. P. Hammett, Physical organic chemistry, (1940), N. Y. 54.

[7] P. Walden, Ber. 35, 2022 (1902).

[8] P. Walden, Z. phys. Chem., 43, 454 (1903).

[9] F. Straus, Liebigs Ann. 370, 338 (1909).

[10] K. H. Meyer, Ber. 41, 2568 (1908).

[11] W. Schlenk, T. Weickel and A. Herzenstein, Liebigs Ann. 372, 10 (1910).

[12] A. Hantzsch, Z. phys. Chem. 1908, 61, 257.

[13] A. Hantzsch, Ber. 54, 2573 (1921).

[14] L. P. Hammett and A. J. Deyrup, J. Am. Chem. Soc. 55, 1900 (1933).

[15] H. A. Smith and R. J. Smith, J. Am. Chem. Soc. 70, 2400 (1948).

[16] C. M. Welch and H. A. Smith, J. Am. Chem. Soc. 72, 4748 (1950).

[17] R. A. Craig, A. B. Garrett and M. S. Newmann, J. Am. Chem. Soc. 72, 163 (1950).

[18] V. Gold, B. N. Hawes and F. L. Tye, J. Chem. Soc. 1952, 2167.

[19] F. Ullmann and A. Münzhuber, Ber. 36, 410 (1903).

[20] H. Frey, Ber. 28, 2514 (1895).

[21] N. D. Pryashnikov. Organic Chemical Practice (State Chem. Press, 1952), 170.

[22] J. U. Nef, Liebigs Ann. 298, 202 (1897).

[23] L. Gattermann and H. Wieland, Practical Organic Chemistry (State Chem. Press, 1948), 378.

[24] J. Troger and O. Beck, J. prak. Chem. 87, 307 (1913).

[25] H. Masson, Compte. rend, 135, 533 (1902).

[26] F. Ullmann and R. Wurstemberg, Ber. 38, 4107 (1905).

[27] Tisser and Grignard, Compt. rend. 132, 1184 (1901).

[28] V. Henry, Phys. Z. 14, 515 (1913).

[29] N. A. Valyashko and N. N. Valyashko, J. Gen. Chem. 18, 1113 (1948).

Received November 9, 1955

Kharkov State University

SPECTRA AND HALOCHROMISM

II. HALOCHROMISM OF TERTIARY ALICYCLIC AND ALIPHATIC ALCOHOLS

V. F. Lavrushin and N. N. Verkhovod

The phenomenon of halochromism has been studied in a large number of aromatic carbinols containing for the most part three aromatic radicals. A few works are devoted to halochromism in aliphatic-aromatic carbinols [1-3]. The halochromism of tertiary alcohols has been very little studied and the opinion has even been expressed [1] that they are incapable of showing halochromism. New data have appeared in the literature in recent years [2, 4, 5], however, on the basis of which it may be assumed that tertiary alcohols are also capable of showing halochromism.

On testing the behavior of different tertiary alcohols in concentrated sulfuric acid we discovered that they formed colored solutions. Since this fact has considerable significance in establishing the relationship between color and the molecular structure of organic compounds we undertook a spectrographic study of the behavior of tertiary alicyclic and aliphatic carbinols in concentrated sulfuric acid.

Tertiary Cyclohexanols

1-Phenylcyclohexanol dissolves only slowly in concentrated sulfuric acid but the yellow color of the solution appears immediately. On illuminating this solution with ultraviolet light a light-green fluorescence appears. The absorption curve of the solution has four absorption Bands (I-IV) (Figure 1, Curve 2).

I		II		III		IV	
λ	ε	λ	ε	λ	ε	λ	ε
4020	10000	3110	980	2700	1900	2280	10000

This absorption curve somewhat resembles the curve for a sulfuric acid solution of dimethylphenylcarbinol but differs from it in the very high intensity of the first band, which has a second broad inflection in the long wave region between 5500 and 4500 A.

1-Cyclohexylcyclohexanol-1 gives a yellow color on addition of concentrated sulfuric acid, but the solution is turbid at first and only becomes transparent after several hours. It shows a light-green fluorescence in ultraviolet light.

The absorption spectra of the sulfuric acid solution were measured 10 hours after addition of the sulfuric acid. The curve obtained has a broad sloping inflection between 5500 and 3500 A, after which comes an intense broad absorption band with a maximum at 3220 A and $\epsilon = 3800$ (Figure 1, Curve 3).

1-Ethylcyclohexanol-1 gives a yellow coloration when concentrated sulfuric acid is added. The initially turbid solution becomes fully transparent after several hours. On illuminating the solution with ultraviolet light a light-green fluorescence is again observed.

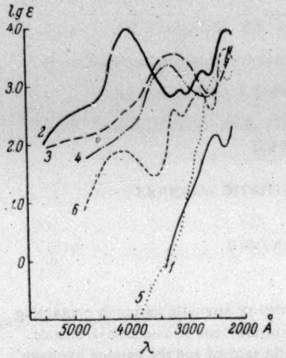


Fig. 1. 1) 1-phenylcyclohexanol-1 in C_2H_5OH, 2) in conc. H_2SO_4, 3) 1-cyclohexylcyclohexanol-1 in conc. H_2SO_4, 4) 1-ethylcyclohexanol-1 in conc. H_2SO_4, 5) dimethylphenylcarbinol in C_2H_5OH, 6) in conc. H_2SO_4.

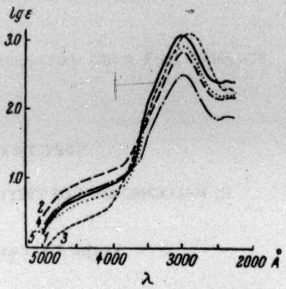


Fig. 2. 1) trimethylcarbinol in conc. H_2SO_4, 2) dimethylethylcarbinol in conc. H_2SO_4, 3) dimethylbutylcarbinol in conc. H_2SO_4, 4) diethylpropylcarbinol in conc. H_2SO_4, 5) diisobutylene in conc. H_2SO_4.

The absorption curve of the sulfuric acid solution (Figure 1, Curve 4) has a broad inflection in the long wave region and a well-defined absorption band in the near ultraviolet with a maximum at 3330 A and ϵ = 2500. The complete curve resembles the absorption curve of 1-cyclohexylcyclohexanol-1 but its absorption band has a narrower peak and lies slightly displaced towards the long-wave region.

Tertiary Alcohols and Diisobutylene

All the tertiary aliphatic alcohols studied dissolved in concentrated sulfuric acid and rapidly formed transparent yellow-colored solutions showing a bright light-green fluorescence in ultraviolet light.

Trimethylcarbinol in sulfuric acid solution gives an absorption curve with a broad inflection between 5000 and 3200 A and an intense absorption band with a maximum at 3000 A and ϵ = 1350. A second scarcely noticeable absorption maximum lies in the short ultraviolet at 2370 A and ϵ = 303 (Figure 2, Curve 1).

Dimethylethylcarbinol in sulfuric acid solution gives an absorption spectrum analogous to that of trimethylcarbinol. Its curve has a more intense inflection between 5000 and 3200 A and a well-defined absorption band of lower intensity with a maximum at 2990 A and ϵ = 740. A poorly-defined maximum is also shown in the shortwave region of the curve at 2380 A and ϵ = 186 (Figure 2, Curve 2).

Dimethylbutylcarbinol in sulfuric acid solution also shows a similar absorption. The curve has an inflection of low intensity between 5000 and 4000 A and a distinct intense absorption band with a maximum at 2910 A and ϵ = 1205. A second poorly-defined absorption maximum lies at 2370 A and ϵ = 220 (Figure 2, Curve 3).

Diethylpropylcarbinol in concentrated sulfuric acid shows an absorption identical with the other carbinols, with an inflection in the long-wave region between 5000 and 3700 A and an absorption band with a maximum at 3000 A and ϵ = 346, after which comes a very weak maximum at 2240 A and ϵ = 15.8 (Figure 2, Curve 4).

Diisobutylene in concentrated sulfuric acid solution behaves like the tertiary aliphatic alcohols and forms a yellow solution which has an intense light-green fluorescence in ultraviolet light.

Its absorption curve also has a broad inflection between 5000 and 3800 A and two absorption maxima. The first of these lies on a distinct intense band at 3000 A and ϵ = 760, while the second is a weak maximum at 2340 A and ϵ = 177 (Figure 2, Curve 5).

When diluted with water, alcohol and other solvents all the sulfuric acid solutions of the compounds studied lost their color and their ability to fluoresce.

Discussion of the Absorption Spectra

The production of color when colorless compounds are dissolved in concentrated sulfuric acid has been called halochromism [6].

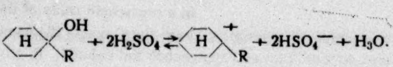
The halochromism of aromatic carbinols has been well studied [7] and involves an acid-base reaction, for example [8, 9]:

$$(C_6H_5)_3COH + 2H_2SO_4 \rightleftarrows [(C_6H_5)C_3]^+ + 2HSO_4^- + H_3O^+.$$

The organic cation formed in this reaction is responsible for the color produced. On comparison of the absorption curves of the acid solutions of the aromatic carbinols with those of their neutral solutions one or several new absorption bands are observed [10, 11].

The behavior in concentrated sulfuric acid of the alicyclic and aliphatic carbinols studied by us is typical of compounds showing halochromic properties.

The appearance of color in the sulfuric acid solutions of these compounds is, in our opinion, similarly connected with the formation of carbonium ions:



$$R_3COH + 2H_2SO_4 \rightleftarrows R_3C^+ + 2HSO_4^- + H_3O^+.$$

On comparison of the absorption spectra of acid solutions of trimethylcarbinol and diisobutylene they are seen to have identical absorption curves. On this basis it may be concluded that for tertiary alcohols formation of more complex carbonium ions is possible, as a result, for example, of further condensation processes. In spite of the fact that this process appears probable [12, 13] it is difficult to resolve the question from absorption curves alone, since other alcohols give identical absorption spectra. Tertiary aliphatic alcohols in general, irrespective of the structure of the radicals present, have apparently the same absorption spectrum.

The question of whether the color of the acid solution is connected with the carbonium ion initially formed or with an ion formed as a result of further changes is not of great importance; the most interesting and important fact in this case is that halochromic properties are shown by tertiary alcohols.

The absorption curves of the sulfuric acid solutions of the carbinols and of diisobutylene diluted with ethyl alcohol have the general absorption characteristics of a solution of diisobutylene in 1.8% sulfuric acid (Figure 3) since the olefin is formed on dilution.

As early as 1909 Oddo and Scandola [14], in a study of the behavior of alcohols in anhydrous sulfuric acid, discovered the formation of yellow or pale yellow colors with a series of alcohols, in contrast to methyl and ethyl alcohols. The yellow color appeared particularly rapidly on dissolving trimethylcarbinol and dimethylethylcarbinol in acid. On pouring these solutions into ice-water the formation of unsaturated hydrocarbons was observed.

Skraup and Freundlich [1] in 1922 observed the formation of a yellow color from the interaction of triisobutylcarbinol with sulfuric acid; they were of the opinion, however, that the phenomenon of halochromism was impossible for aliphatic compounds since in such cases the possibility of formation of a quinonoid radical is excluded. In subsequent years a number of works appeared showing that this view was mistaken.

Thus, in 1932 the formation of a red color was observed in an aqueous solution of tripropenylcarbinol under the influence of H-ions [15]. In later work Gordon and Burwell [16, 17] and D. N. Kursanov and co-workers [18, 19] established that saturated hydrocarbons, even when containing only one tertiary carbon atom, form solutions in sulfuric acid varying in color from yellow to red.

It has been confirmed by ourselves, D. N. Kursanov and V. N. Setkina [4] that the color of these solutions is connected with the oxidation of the hydrocarbons and the formation of carbonium salts, whose cation is responsible for the halochromic properties of the solutions. In addition, it was discovered by D. N. Kursanov and V. N. Setkina [20] that aliphatic ketones also give yellow-orange solutions in concentrated sulfuric acid. The color of these solutions disappears on pouring into water or on neutralization with soda.

In 1953 Welch and Smith [5], studying the decomposition of diphenylacetic acid and its derivatives by the action of sulfuric acid according to the equation

$$(C_6H_5)_2CHCOOH + 2H_2SO_4 \rightleftharpoons [(C_6H_5)_2CH]^+ + 2HSO_4^- + H_3O^+ + CO,$$

observed the formation of yellow and red-orange colors and the separation of up to 65% CO for dicyclohexylacetic acid.

The formation of the trimethylcarbonium cation from the interaction of the appropriate esters or of trimethylcarbinol itself with sulfuric acid has been postulated many times [21-23].

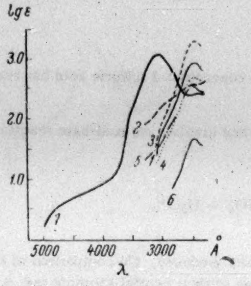


Fig. 3. After dilution of the sulfuric acid solutions with C_2H_5OH. 1) trimethylcarbinol, 2) dimethylethylcarbinol, 3) dimethylbutylcarbinol, 4) diethylpropylcarbinol, 5) diisobutylene, 6) diisobutylene in 1.8% H_2SO_4 in C_2H_5OH, 7) trimethylcarbinol in conc. H_2SO_4.

In a cryoscopic study of the behavior of trimethylcarbinol in sulfuric acid at temperatures below 14°, Newman, Craig and Garrett [22] found that the initial value 2.3 of the coefficient obtained increased with time and approached the value 4. In our opinion this may come about as a result of processes which the authors have considered improbable for tertiary aliphatic alcohols:

$$(CH_3)_3COH + H_2SO_4 \rightleftarrows (CH_3)_3COH_2^+ + HSO_4^-,$$
$$(CH_3)_3COH_2^+ \rightleftarrows (CH_3)_3C^+ + H_2O,$$
$$H_2O + H_2SO_4 \rightleftarrows H_3O^+ + HSO_4^-.$$

These processes may be summarized by the equation:

$$(CH_3)_3COH + 2H_2SO_4 \rightleftarrows (CH_3)_3C^+ + 2HSO_4^- + H_3O^+.$$

The fact that at a higher temperature after a much longer period of time the isotonic coefficient becomes approximately 5 may be connected with further changes undergone by the trimethylcarbonium ion. Thus on cryoscopic study of diphenylcarbinol in sulfuric acid values of the isotonic coefficient of the order of 5.0-6.1 were obtained after 24 hours, yet this does not lead one to doubt the possibility of the formation of the diphenylcarbonium ion under these conditions [24].

Confirmation that the color belongs to a carbonium ion is provided by the recently achieved synthesis of tropyl bromide and chloride which have the properties of salts. The yellow color of the tropyl ion, like that of the sulfuric acid solutions of tertiary alcohols, arises in the long wave region of the absorption curve [25].

Synthesis and Purification of Specimens

The 1-phenylcyclohexanol-1 was synthesized from phenyl magnesium bromide and cyclohexanone [26]. The purified specimen melted at 62.5-63.0°, which agrees with the literature data [27].

The 1-cyclohexylcyclohexanol-1 was synthesized from cyclohexyl magnesium bromide and cyclohexanone [26]. After repeated recrystallization the specimen melted at 50.5-51.0°.

The 1-ethylcyclohexanol-1 was prepared from ethyl magnesium iodide and cyclohexanone [26]. After vacuum distillation the product was purified on an alumina chromatographic column, n_D^{20} 1.4610.

Kalbaum's trimethylcarbinol was redistilled and the fraction with b.p. 83° was collected. After freezing out it was purified by chromatographic absorption on alumina. Since in this process the trimethylcarbinol is displaced by water, it was obtained as a molecular compound with water, b.p. 80.0° [28], n_D^{20} 1.3860.

The dimethylethylcarbinol was synthesized from ethyl magnesium iodide and acetone [29]. The fraction collected at 102° was purified chromatographically on alumina, n_D^{20} 1.4060.

The dimethylbutylcarbinol was obtained from butyl magnesium bromide and acetone. The fraction distilling at 140° [30] was collected and purified by chromatographic absorption, n_D^{20} 1.4220.

The diethylpropylcarbinol was synthesized from ethyl magnesium iodide and methyl butyrate [31]. The fraction collected at 160° was afterwards purified on a chromatographic column, n_D^{20} 1.4175.

The diisobutylene was synthesized from trimethylcarbinol by warming on a water bath with dilute (1:1) sulfuric acid [13]. The fraction distilling at 103.5° was collected and subsequently purified by chromatography on alumina, n_D^{20} 1.4110.

From the Raman scattering spectra of diisobutylene it was established that it consisted of a mixture of approximately equal quantities of 2,4,4-trimethylpentene-1 and 2,4,4-trimethylpentene-2 [32].

The absorption spectra of the alicyclic carbinols were measured by the photographic method on the quartz spectrograph ISP-22. The spectra of the tertiary aliphatic carbinols were measured using the spectrophotometer with photoelectric recorder SPH-4.

In conclusion we have to express our gratitude to A. N. Terenin for interest shown in the work and for valuable advice given.

SUMMARY

1. The absorption spectra of 1-phenylcyclohexanol-1, 1-cyclohexylcyclohexanol-1, 1-ethylcyclohexanol-1, trimethylcarbinol, dimethylethylcarbinol, dimethylbutylcarbinol, diethylpropylcarbinol and diisobutylene in concentrated sulfuric acid have been studied.

2. It has been established that all the compounds studied have a characteristic absorption spectrum in the visible region.

3. From the behavior of the acid solutions, their absorption spectra and the literature data it is concluded that the cause of the color of the sulfuric acid solutions of tertiary alicyclic and aliphatic alcohols is the formation of carbonium ions by an acid-base reaction.

LITERATURE CITED

[1] S. Skraup and F. Freundlich, Ber. 55, 1073 (1922).

[2] V. F. Lavrushin, Bull. Acad. Sci. USSR, phys. ser. 17, 723 (1953).

[3] V. F. Lavrushin, Proc. Acad. Sci. USSR 86, 309 (1952).

[4] V. F. Lavrushin, D. N. Kursanov and V. N. Setkina, Proc. Acad. Sci. USSR 97, 265 (1954).

[5] C. M. Welch and H. A. Smith, J. Am. Chem. Soc. 75, 1412 (1953).

[6] A. Bayer and V. Villiger, Ber. 35, 1189 (1902).

[7] L. P. Hammett, Physical organic chemistry, 1940, N. Y., 54.

[8] L. P. Hammett and A. J. Deyrup, J. Am. Chem. Soc. 55, 1900 (1933).

[9] V. Gold, B. W. Hawes and F. L. Tyl, J. Chem. Soc. 1952, 2167.

[10] L. C. Anderson, J. Am. Chem. Soc. 52, 4567 (1930).

[11] V. Gold, and F. Tyl, J. Chem. Soc. 1952, 2172.

[12] A. M. Butlerov, J. Russ. Phys.-Chem. Soc. 11, 197 (1879).

[13] C. O. Tonberg, J. D. Pickens, M. R. Fenskea and C. Whitmore, J. Am. Chem. Soc. 54, 3707 (1932).

[14] G. Oddo and E. Scandola, Gazz. 39, 2, 1 (1909); Chem. Zentr. 1909, 2, 2114.

[15] Ch. Prevort, Compt. rend. 195, 1082 (1932).

[16] R. L. Burwell and G. S. Gordon, J. Am. Chem. Soc. 70, 3128 (1948).

[17] G. S. Gordon and R. L. Burwell, J. Am. Chem. Soc. 71, 2355 (1949).

[18] V. N. Setkina, D. N. Kursanov, O. D. Sterligov and A. L. Liebermann, Proc. Acad. Sci. USSR 85, 1045 (1952).

[19] D. N. Kursanov, V. N. Setkina and O. D. Sterligov, Bull. Acad. Sci. USSR, Div. Chem. Sci. 1953, 1035.

[20] D. N. Kursanov and V. N. Setkina, Proc. Acad. Sci. USSR, 94, 69 (1954).

[21] S. G. Cohen and A. Scheiden, J. Am. Chem. Soc. 63, 3382 (1941).

[22] M. S. Newman, R. A. Craig and A. B. Garrett, J. Am. Chem. Soc. 71, 869 (1949).

[23] L. P. Kuhn, J. Am. Chem. Soc. 71, 1575 (1949).

[24] C. M. Welch and H. A. Smith, J. Am. Chem. Soc. 72, 163 (1950).

[25] W. E. Doering, L. H. Knox, J. Am. Chem. Soc. 76, 3203 (1954).

[26] P. Sabatier and A. Mailhe, Compt. rend. 138, 1322 (1904).

[27] N. Kursanov, J. Russ. Phys.-Chem. Soc. 38, 1301 (1906).

[28] A. M. Butlerov, J. Russ. Phys.-Chem. Soc. 3, 154 (1871).

[29] N. D. Pryashnikov, Organic Chemical Practice (State Chem. Press, 1952), 171.

[30] L. Henri, Compt. rend, 143, 103 (1906).

[31] H. Masson, Compt. rend. 132, 484 (1901).

[32] E. S. Gross, K. V. Nelson and Ya. M. Slobodin, J. Phys. Chem. 25, 506 (1951).

Received November 9, 1955

Kharkov State University

CATALYTIC REACTIONS WITH METALLIC ALUMINUM

II. ALKYLATION OF BENZENE WITH CHLOROCYCLOHEXANE AND CHLOROCYCLOPENTANE

M. B. Turova-Polyak and I. R. Davydova

The catalytic synthesis of cyclohexylbenzene was first carried out by N. I. Kursanov [1] by alkylation of benzene with chlorocyclohexane in the presence of aluminum chloride. At present the catalytic synthesis of cyclohexylbenzene is carried out by alkylation of benzene with cyclohexene in the presence of aluminum chloride [2-4], sulfuric acid [4] and hydrogen fluoride [5], as well as by alkylation of benzene with cyclohexanol in the presence of aluminum chloride [6] and boron fluoride [7].

Besides that, cyclohexylbenzene was obtained by alkylation of benzene with cyclohexene in the presence of metallic aluminum with the addition of butyl chloride [8].

S. S. Nametkin [9] was the only one to obtain cyclopentylbenzene catalytically by alkylation of benzene with cyclopentene in the presence of aluminum chloride.

In developing our investigations on alkylation of benzene with halogen derivatives in the presence of metallic aluminum [10], we decided to study the alkylation of benzene with chlorocyclohexane and chlorocyclopentane. In this work we were able to find conditions under which the cyclohexyl- and cyclopentylbenzene yields reached 90-95% on the chloro derivative used for the reaction.

We showed in this work that 0.015 g-atom of metallic aluminum per 1 mole of chloro derivative was sufficient for the reaction. However, a part of the aluminum remained unused even with such a ratio of reacting components. The unreacted metallic aluminum may be used again and in its presence the monoalkylbenzene yield increased almost twice. This is explained by the fact that the surface of the metallic aluminum was activated by the hydrogen and aluminum chlorides formed in the reaction process.

We further established that an increase in benzene concentration in the reaction mixture favored a higher monoalkylbenzene yield. An increase in yield of polyalkylbenzenes – dicyclohexyl- and dicyclopentylbenzenes – was observed on increasing the concentration of chloro compounds in the reaction mixture. The dialkylbenzenes consisted of para- and meta-isomers. The para-isomer content was increased by a decrease in the concentration of chloro compounds in the original mixture, while the meta-isomer content was increased with an increase in concentration of chloro compounds. o-Dicyclohexyl- and o-dicyclopentylbenzenes were not found in the reaction products. By considerably increasing the concentration of the chloro compounds mainly polycyclohexyl- and polycyclopentyl-benzenes may be obtained.

A raise in reaction temperature favors an increased polyalkylbenzene yield. A lower temperature and thus a lower reaction rate favors an increased monoalkylbenzene yield.

The advantages and special features of the method for obtaining cyclohexyl- and cyclopentylbenzenes in the presence of metallic aluminum developed by us, as compared with those mentioned above [1-9], consist of the following: a high yield of alkylation products, use of small amounts of metallic aluminum, possibility of directing the reaction either toward obtaining monosubstituted or polysubstituted benzenes, the simplicity of isolating the individual reaction products and the absence of side-reactions.

EXPERIMENTAL

The chlorocyclohexane, required for the reaction, was prepared from cyclohexanol and concentrated hydrochloric acid [11] in 88% yield. The constants of the chlorocylohexane – b.p. 142-143° (760 mm), n_D^{20} 1.4629, d_4^{20} 1.0000 – agreed with those reported in the literature: b.p. 142° (750 mm) [12], n_D^{20} 1.4624 [13], d_4^{20} 1.0000 [13].

Similarly, chlorocylopentane was prepared from cyclopentanol and concentrated hydrochloric acid in 82% yield and had b.p. 115° (760 mm) n_D^{20} 1.4511, d_4^{20} 1.0048. N. D. Zelinsky [14] reported for chlorocyclopentane b.p. 114-115.5° (760 mm), n_D^{20} 1.4510, d_4^{20} 1.0051. The benzene (thiophen free) had b.p. 80° (760 mm), n_D^{20} 1.5010, d_4^{20} 0.8790.

The reactions were carried out in an apparatus described in a previous paper [10]. The starting materials were carefully dried and distilled immediately before the experiment. The metallic aluminum was cut on a lathe, also immediately before the experiment, and stored under dry benzene.

In the alkylation of benzene with chlorocyclohexane and chlorocyclopentane, the reaction mixture was heated on a water bath to the boiling point of the mixture (85-90°). The duration of the preliminary heating (induction period) depended on the proportions of the components taken (10-15 minutes).

The appearance of bubbles of hydrogen chloride indicated the beginning of the reaction. If heating of the reaction mixture on the water bath was continued, the reaction proceeded extremely vigorously (athough the temperature fell to 70-72°), was complete in a few minutes and was accompanied by the copious evolution of hydrogen chloride. The reaction mixture, which was originally colorless, became a dark orange color.

When the reaction was complete, the mixture was heated for a further 10-15 minutes until the evolution of hydrogen chloride ceased.

On cooling, the reaction product, which was a clear, mobile liquid, was decomposed with hydrochloric acid, dried with calcium chloride and fractionated several times.

The yields of the alkylation products were calculated on the chlorocyclohexane and chlorocyclopentane taken.

The Effect of the Ratio of the Reaction Components on the Yield of Cyclohexylbenzenes

This series of experiments (Table 1) was carried out with various molar ratios of benzene and chlorocyclohexane from 1:2 to 20:1 in the presence of 0.05 g-at of aluminum to 1 mole of chlorocyclohexane.

The following fractions were isolated by distilling the alkylation products: 1st, excess benzene, 2nd, 236-240° (760 mm) – cyclohexylbenzene, 3rd, 240-365° (760 mm) – dicyclohexylbenzenes.

After a second distillation over metallic sodium, the fraction from 236-240° boiled at 237.5-238.8° (760 mm) and had the constants:

n_D^{20} 1.5262, d_4^{20} 0.9424, MR_D 52.22; calc.: 51.81.

According to Evans [15], cyclohexylbenzene has the following constants: b.p. 239 ±.6° (760 mm), n_D^{20} 1.5260, d_4^{20} 0.9428.

The fraction with b.p. 240-365° – dicyclohexylbenzenes – was a mixture of a rather thick oil and crystals, whose composition varied with the molar ratio of the starting materials. The crystals were filtered off on a sintered glass filter and after recrystallization from alcohol they melted at 101-102°, which corresponds to p-dicyclohexylbenzene.

Found %: C 89.07, 89.01; H 10.93, 10.90. $C_{18}H_{26}$. Calculated %: C 89.18; H 10.82.

Nametkin [3] and Braun [16] report m.p. 101-102° for p-dicyclohexylbenzene.

After some time the oily liquid yielded another crop of crystals with m.p. 101-102°. The remaining oil distilled at 325-335° (760 mm) [201-202° (14 mm)] and had constants corresponding to m-dicyclohexylbenzene:

n_D^{20} 1.5367, d_4^{20} 0.9710, MR_D 77.92; calc.: 77.32. Found %: C 89.29, 89.37; H 10.74, 10.66. $C_{18}H_{26}$. Calculated %: C 89.18; H 10.82.

According to Nametkin [3], m-dicyclohexylbenzene has b.p. 165-168° (3.5 mm), n_D^{20} 1.5362, d_4^{20} 0.9668.

With component ratios of 2 : 1 and 1 : 1, the reaction proceeded somewhat differently than in the other experiments: besides the oily product, fine crystals settled in the bottom of the flask. After recrystallization from benzene they melted at 264-265° and corresponded to 1,2,4,5-tetracyclohexylbenzene.

Found %: C 89.45, 89.40; H 11.48, 11.49. $C_{30}H_{46}$. Calculated %: C 88.59; H 11.41.

Nametkin [3] reported m.p. 265° for 1,2,4,5-tetracyclohexylbenzene.

The liquid product was examined as in all the rest of the experiments and consisted of monocyclohexylbenzene and a mixture of dicyclohexylbenzenes.

The formation of only p- and m-dicyclohexylbenzenes from benzene and cyclohexene, chlorocyclohexane and cyclohexanol is mentioned in the papers of Nametkin [3], McKenna [7] and Braun [16].

TABLE 1

The Effect of the Ratio of the Reaction Components on the Yield of Cyclohexylbenzenes

Ratio C_6H_6 : $C_6H_{11}Cl$ (in moles)	Induction period (in min)	Yield of cyclohexylbenzenes (in %)		Composition of the polycyclohexylbenzene fraction (in weight %)		
		monocyclohexylbenzene	polycyclohexylbenzene	p-dicyclohexylbenzene	m-dicyclohexylbenzene	tetracyclohexylbenzene
1:2	1-2*	5	86	–	20	80
1 : 1	3	16	64	–	92	8
2 : 1	4	24	67	–	–	–
4 : 1	10	40	53	30	70	–
5 : 1	10	46	39	–	–	–
6 : 1	10	57	37	50	50	–
7 : 1	13	59	33	62	38	–
10 : 1	20	61	32	–	–	–
15 : 1	30	70	24	–	–	–
20 : 1	60	72	21	–	–	–

---

* The mixture was heated at its boiling point on an oil bath; in all other cases the mixture was heated on a water bath.

The Effect of the Ratio of the Reaction Components on the Yield of Cyclopentylbenzenes

The experiments were carried out with mixtures of benzene and chlorocyclopentane, in ratios of from 2 : 1 to 15 : 1 in the presence of 0.05 g-at of metallic aluminum to 1 mole of chlorocyclopentane (Table 2).

The following fractions were isolated by distilling the reaction products: 1st, excess benzene, 2nd, 216-220° – cyclopentylbenzene, 3rd, 220-315° – dicyclopentylbenzenes.

In the experiment with a ratio of benzene: chlorocyclopentane of 2 : 1, a 4th fraction with b.p. 315-365° was isolated.

After a second distillation over metallic sodium, the fraction from 216-220° had the following constants:

b.p. 217-219° (760 mm), n_D^{20} 1.5290, d_4^{20} 0.9466, MR_D 47.73; calc. 47.20. Evans data [15] for cyclopentylbenzene: b.p. 219-220 ± 0.5° (760 mm), n_D^{20} 1.5280, d_4^{20} 0.9462.

The fraction with b.p. 220-315° was a viscous liquid at normal temperatures and on cooling to –17° it partly crystallized. The crystals which separated were quickly filtered off on a sintered glass filter. The operation was repeated until no more crystals separated. After recrystallization from alcohol, we isolated p-dicyclopentylbenzene with m.p. 44-45°.

Found %: C 89.37, 89.41; H 10.57, 10.51. $C_{16}H_{22}$. Calculated %: C 89.64; H 10.36.

Nametkin [9], who first isolated this hydrocarbon, reported m.p. 42-43° for it.

The residual oily hydrocarbon was distilled twice over sodium at 304-305° (760 mm) and had constants which were close to those of m-dicyclopentylbenzene:

n_D^{20} 1.5410, d_4^{20} 0.9790, MR_D 68.81; calc. 68.19. Found %: C 89.38, 89.42; H 10.50, 10.43. $C_{16}H_{22}$. Calculated %: C 89.64; H 10.36.

m-Dicyclopentylbenzene was first isolated and characterized by Nametkin [9]: b.p. 154-156° (4 mm), n_D^{20} 1.5409, d_4^{20} 0.9805.

TABLE 2

The Effect of the Ratio of the Components on the Yield of Cyclopentylbenzenes

Ratio C_6H_6 : C_5H_9Cl (in moles)	Induction period (in min)	Yield of alkylbenzenes (in %)	
		monocyclopentylbenzene	polycyclopentylbenzene
2 : 1	3	19	63
5 : 1	6	44	40
7 : 1	6	50	41
10 : 1	15	56	35
15 : 1	45	62	23

In the experiment with a molar ratio of the reaction components of 2 : 1, on cooling the fraction with b.p. 315-365° to −17°, crystals separated immediately. They were isolated and after recrystallization from alcohol, they melted at 61-62° and corresponded to tricyclopentylbenzene [9].

Found %: C 89.50, 89.47; H 10.83, 10.79. $C_{21}H_{30}$. Calculated %: C 89.29; H 10.71.

The liquid remaining after the separation of tricyclopentylbenzene was a mixture of p- and m-dicyclopentylbenzenes.

In the alkylation of benzene with cyclopentene in presence of aluminum chloride, Nametkin [9] also did not detect the orthoisomer of dicyclopentylbenzene.

The Effect of the Amount of Metallic Aluminum on the Yield of Cyclohexyl- and Cyclopentylbenzenes

In all the preceding experiments, at the end of the reaction a large part of the metallic aluminum remained unused; therefore we carried out some experiments using a smaller (by 2-3 times) amount of aluminum. However, it was shown that the smaller amount of aluminum, down to 0.015 g-at of aluminum to 1 mole of chloro derivative, affected neither the yield nor the composition of the reaction products (Table 3).

TABLE 3

The Effect of the Amount of Aluminum on the Yield of Alkylation Products

Ratio C_6H_6 : $C_6H_{11}Cl$ and C_6H_6 : C_5H_9Cl (in moles)	Amount of aluminum (in g-at per 1 mole of chloro derivative)	Yield (in %)			
		monocyclohexylbenzene	dicyclohexylbenzene	monocyclopentylbenzene	dicyclopentylbenzene
5 : 1	0.05	46	39	44	39
5 : 1	0.025	46	38	45	40
5 : 1	0.015	47	38	45	40
7 : 1	0.05	59	33	50	41
7 : 1	0.025	59	33	49	40
7 : 1	0.015	57	32	50	41

The Effect of Activation of the Aluminum on the Yield of Cyclohexylbenzene and Cyclopentylbenzene

If we took the aluminum remaining from a previous experiment, which had a rough surface and was covered with a thin layer of a viscous brown material (complex), and at once added it to a new portion of starting materials, then the reaction began immediately and was accompanied by the evolution of hydrogen chloride and heating up of the mixture to 28-30°. The reaction was complete in approximately one hour.

Using aluminum activated in this way, the yield of monocyclohexyl- and monocyclopentylbenzenes was sharply increased in comparison with experiments carried out with freshly cut aluminum turnings (Table 4).

TABLE 4

The Effect of Activation of the Aluminum on the Yield of Alkylation Products

Ratio $C_6H_6 : C_6H_{11}Cl$ and $C_6H_6 : C_5H_9Cl$ (in moles)	Nature of the catalyst (of the aluminum)	Yield of alkylation products (in %)			
		monocyclohexylbenzene	dicyclohexylbenzene	monocyclopentylbenzene	dicyclopentylbenzene
5 : 1	Freshly cut turnings	47	39	44	39
5 : 1	Activated	80	16	88	13
7 : 1	Freshly cut turnings	59	33	50	41
7 : 1	Activated	85	10	86	4

The Effect of the Reaction Temperature on the Yield of Cyclohexyl- and Cyclopentylbenzenes

The reaction method was varied slightly to elucidate this problem. The reaction mixture was heated on a water bath to the beginning of the reaction (evolution of the first bubbles of hydrogen chloride). Thereupon the heating was discontinued; the temperature fell from 85-90° to 28-30° and the reaction proceeded slowly for 1.5-2 hours.

TABLE 5

The Effect of Temperature on the Yield of Alkylation Products

Ratio $C_6H_6 : C_6H_{11}Cl$ and $C_6H_6 : C_5H_9Cl$ (in moles)	Yield (in %)			
	of monocyclohexylbenzene by carrying out the experiment		of monocyclopentylbenzene by carrying out the experiment	
	with heating	without heating after the beginning of the reaction	with heating	without heating after the beginning of the reaction
5 : 1	46	69	44	78
7 : 1	59	80	50	83

Under these conditions the yield of monoalkylbenzenes increased significantly (Table 5) and the dialkylbenzenes formed consisted almost entirely of the para isomers.

SUMMARY

1. The possibility of alkylation of benzene with chlorocyclohexane and chlorocyclopentane in the presence of metallic aluminum was shown.

2. The yield of cyclohexylbenzenes and cyclopentylbenzenes reached 90-95% on the chloro derivative taken for the reaction.

3. Conditions were found under which it was possible to obtain either mono- or polycyclohexyl- and cyclopentylbenzenes.

LITERATURE CITED

[1] N. I. Kursanov, Liebigs Ann. 318, 309 (1901).

[2] D. Bodroux, Ann. Chim., (10) 11, 511 (1929).

[3] S. S. Nametkin and E. S. Pokrovskaya, J. Gen. Chem. 7, 962 (1937).

[4] B. B. Corson and V. N. Ipatieff, J. Am. Chem. Soc. 59, 645 (1937).

[5] J. H. Simons and S. Archer, J. Am. Chem. Soc. 60, 2952 (1938).

[6] I. P. Tsukervanik and N. G. Sidorova, J. Gen. Chem. 7, 641 (1937).

[7] J. F. McKenna and F. J. Sowa, J. Am. Chem. Soc. 59, 470 (1937).

[8] N. G. Sidorova, I. P. Tsukervanik and Z. Kh. Abidova, Proc. Acad. Sci. Uzbek SSR 5, 33 (1953).

[9] S. S. Nametkin and E. S. Pokrovskaya, J. Gen. Chem. 8, 699 (1938).

[10] M. B. Turova-Polyak and M. A. Maslova, J. Gen. Chem. 26, 2185 (1956).

[11] J. F. Norris, R. S. Mulliken, J. Am. Chem. Soc., 42, 2097 (1920).

[12] W. Markownikoff, Liebigs Ann. 302, 9 (1898).

[13] M. S. Kharasch, H. C. Brown, J. Am. Chem. Soc. 61, 2142 (1939).

[14] N. Zelinsky, Ber. 41, 2627 (1908)

[15] E. B. Evans, J. Inst. Petroleum Techn. 24, 537 (1938).

[16] I. Braun, Ber. 60, 1180 (1927).

Received October 20, 1955

Moscow State University

HYDROGENATION AND HYDROGENOLYSIS OF α-ETHYL AND α-PROPENYLFURAN ON RANEY NICKEL CATALYST

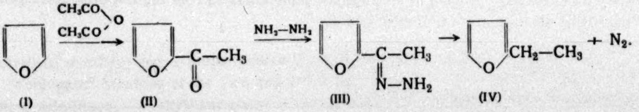
N. I. Shuikin and I. F. Belsky

We had shown in a previous paper [1] that an unusual hydrogenolysis of the furan ring occurred during the hydrogenation of furan and sylvan on a Raney nickel catalyst. Besides the products, formed as a result of the splitting of the furan ring at the C−O bonds, there was a compound in the catalyzate whose formation required coupled ("conjugated") breaking of the C−O and C−C-bonds in the furan ring. We also considered the possibility of the formation of alcohols with a lower number of carbon atoms than in furan or sylvan; furthermore, the hypothesis on the "conjugated" breaking of the furan ring was experimentally confirmed. α-Ethyl- and α-propenylfurans were used in this work for investigations of this kind. Conditions were found for the comparatively smooth conversion of these compounds into the corresponding tetrahydro derivatives, and their hydrogenolysis was studied on a Raney nickel catalyst.

EXPERIMENTAL

The hydrogenation of α-ethyl- and α-propenylfuran was carried out by the circulating method in the presence of Raney nickel, which we used previously [1] for the hydrogenation of furan and sylvan. The method of carrying out the experiments was the same as in the previous work.

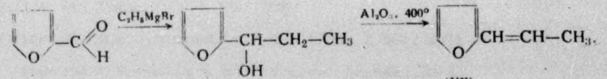
Synthesis of α-ethylfuran according to the scheme:



The acetylation of furan with acetic anhydride using hydriodic acid as the catalyst was carried out as described in paper [2]. The α-acetylfuran (II) was obtained in 70% yield and had b.p. 46-48° (7 mm) and m.p. 30-31°. α-Acetylfuran hydrazone (III) was prepared by boiling a solution of (II) and hydrazine hydrate in ethyl alcohol on a water bath for 5-6 hours. After distilling off the alcohol and water (temperature of liquid not less than 100°), the hydrazone was dried with calcium chloride and decomposed. We established that it was possible to use nickel deposited on aluminum oxide (30% Ni) for decomposing the hydrazone instead of platinum. To obtain high yields of α-ethylfuran (IV) (up to 75-80%) it was necessary to fulfill several conditions. The hydrazone had to be carefully dried; the caustic potash, used for decomposing the hydrazone, had to be roasted to free it from traces of moisture; the decomposition had to be carried out slowly as a vigorous reaction produced tar and considerably lowered the yield of the final product. The α-ethylfuran obtained was distilled on a column with an efficiency of 30 theoretical plates:

b.p. 91-91.5° (750 mm), d_4^{20} 0.9018, n_D^{20} 1.4402, MR$_D$ 28.11, C_6H_8O; calc. 28.42.

Synthesis of α-propenylfuran was carried out by the following scheme:



(V) (VI) (VII)

Pure α-propenylfuran (VII) was isolated by distilling the dehydration product on a column with an efficiency of 30 theoretical plates:

b.p. 132-133° (752 mm), n_D^{20} 1.5098, d_4^{20} 0.9457, MR_D 34.02, C_7H_8O; calc. 32.57.

Catalytic hydrogenation of α-ethylfuran and α-propenylfuran. α-Ethylfuran, in portions of 125 g, was hydrogenated at 175 and 225° at a volume rate of 0.06 in excess hydrogen. α-Propenylfuran, in similar portions, was hydrogenated at the same volume rate at 135 and 175°. After hydrogenating both the compounds, the activity of the catalyst was practically unchanged. At 175° the α-ethylfuran was converted into α-ethyltetrahydrofuran in 80% yield. Raising the temperature to 225° lowered the yield of α-ethyltetrahydrofuran to 40% and correspondingly increased the amount of products of hydrogenolysis of the furan ring. The α-ethyltetrahydrofuran possessed the following constants:

b.p. 106.5-107° (742 mm), d_4^{20} 0.8556, n_D^{20} 1.4163, MR_D 29.27, $C_6H_{12}O$; calc. 29.35.

α-Propenylfuran showed a significantly lower resistance to hydrogenolysis than α-ethylfuran or sylvan [1]. At 175° it was cleaved to 85-90%; at 135° α-propenylfuran was almost quantitatively hydrogenated to α-n-propenyltetrahydrofuran, which boiled at 131.5-132.5° (750 mm).

d_4^{20} 0.8562, n_D^{20} 1.4232, MR_D 33.98. $C_7H_{14}O$. calc. 33.97.

The study of the hydrogenolysis products of α-ethyl- and α-propenylfuran was quite interesting in connection with the observations that we had made previously on the hydrogenation of furan and sylvan; therefore we carefully studied the products of hydrogenolysis of the furan ring. We separated them into narrow fractions and prepared benzoates for those corresponding to alcohols, and semicarbazones for the fractions corresponding to ketones. The analytical data are given in Tables 1, 2 and 3.

TABLE 1.*

Hydrogenolysis Products of α-Ethylfuran at 175°

Hydrogenolysis products	Content in catalyzate (in %)	Boiling point (corr.)	d_4^{20}	n_D^{20}	Melting point of benzoate	Melting point of semicarbazone
Pentanol-3	23	114-115°	0.8175	1.4136	383-385°	–
Hexanone-3	8	123-124	0.8160	1.4002	–	109-110°
Hexanol-3	67	134-134.5	0.8194	1.4150	–	–
Hexanol-1	2	157-159	0.8243	1.4182	404-406	–

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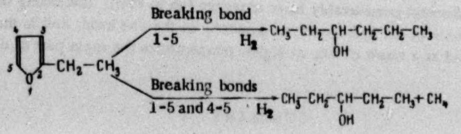
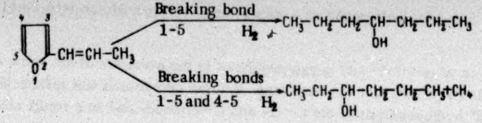
* In Tables 1, 2 and 3 we took the total amount of hydrogenolysis products of α-ethyl- and α-propenylfuran as 100%.

In accordance with the scheme which we put forward earlier [1], the formation of alcohols with a smaller number of carbon atoms, than in the original alkylfuran, arises from the conjugate breaking of C–O and C–C bonds, with the elimination of one CH group:


Breaking bond
1-5
H_2
$CH_3-CH_2-CH(OH)-CH_2-CH_2-CH_3$
CH_2-CH_3
Breaking bonds
1-5 and 4-5
H_2
$CH_3-CH_2-CH(OH)-CH_2-CH_3+CH_4$


Breaking bond
1-5
H_2
$CH_3-CH_2-CH_2-CH(OH)-CH_2-CH_2-CH_3$
$CH=CH-CH_3$
Breaking bonds
1-5 and 4-5
H_2
$CH_3-CH_2-CH(OH)-CH_2-CH_2-CH_3+CH_4$

Thus, in the hydrogenolysis of α-ethyl- and α-propenylfuran, we found the same mechanism for the hydrogenolysis of the furan ring, as in the case of furan and sylvan. As was to be expected, the shielding effect of the ethyl and propenyl groups for the neighboring C–O and C–C bonds was considerably greater than the effect of the methyl group in sylvan. As a result of this, in the hydrogenation of α-ethyl- and α-propenylfuran we did not observe conjugate breaking of the 1–2 and 2–3, 1–5 and 2–3 and 1–2 and 4–5 bonds, while in the hydrogenation of sylvan, the latter two forms of bond breaking gave rise to ethyl and methyl alcohols.

TABLE 2

Hydrogenolysis Products of α-Ethylfuran at 225°

Hydrogenolysis product	Content in catalysate (in %)	Boiling point (corr.)	d_4^{20}	n_D^{20}	Melting point of semicarbazone
Pentanone-3	27	101—102°	0.8165	1.3998	136.5—137.5°
Hexanone-3	70	123—124	0.8169	1.4006	109 —110
Hexanol-3	3	157—160	0.8253	1.4190	—

Hydrogenolysis of α-ethyl- and α-propenylfuran proceeds mainly through the breaking of the C–O bond (1–5) and the "conjugate" breaking of the 1–5 and 4–5 bonds. The 1–2 C–O bond is broken only to a very slight degree in α-ethylfuran. α-Ethylfuran shows a considerably higher resistance to hydrogenolysis than furan or sylvan.

TABLE 3

Hydrogenolysis Products of α-Propenylfuran at 175°

Hydrogenolysis products	Content in catalysate (in %)	Boiling point (corr.)	d_4^{20}	n_D^{20}	Melting point of semicarbazone
Hexanone-3	22	123—124°	0.8148	1.4011	109.5—110°
Hexanol-3	18	133—135	0.8172	1.4162	—
Heptanone-4	31	142—142.5	0.8192	1.4080	132 —132.5
Heptanol-4	29	153—154	0.8196	1.4204	—

The same degree of furan ring cleavage (15-20%) occurred in the case of sylvan at 125° as in the case of α-ethylfuran at 175°. At 225° the hydrogenolysis products of α-ethylfuran formed about 60% of the catalyzate, while at only 200° sylvan underwent considerably more cleavage (up to 80%). Increasing the reaction temperature showed up in an overall increase in the hydrogenolysis products, on the one hand, and in the conversion of alcohols into ketones, on the other, and as a result of this, at higher temperatures the main part of the catalyzate consisted of ketones.

SUMMARY

1. Conditions were found for hydrogenating α-ethyl- and α-propenylfuran into their tetrahydro derivatives on Raney nickel catalyst.

2. The hydrogenolysis of α-ethyl- and α-propenylfuran in the presence of the same catalyst was investigated at various temperatures. It was shown that the furan ring in these compounds was split at the C–O bond as well as undergoing "conjugated" hydrogenolysis of the C–O- and C–C-bonds and as a result alcohols and ketones were formed with a lower number of carbon atoms than in the original materials.

3. The different stabilities of the C–O- and C–C bonds to hydrogenolysis was due to the shielding action of side substituents on neighboring bonds.

LITERATURE CITED

[1] N. I. Shuikan, V. A. Tulupov and I. F. Belsky, J. Gen. Chem. 25, 1175 (1955).(T.p. 1125).*

[2] H. Hartough and A. Kosak, J. Am. Chem. Soc. 68, 2639 (1946).

Received November 1, 1955

Institute of Organic Chemistry of the
Academy of Science of the USSR

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* T.p = C. B. Translation pagination.

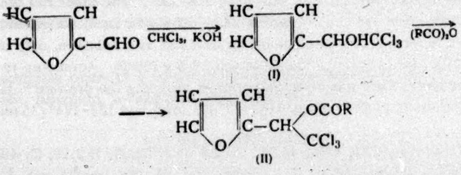
2-FURYLTRICHLOROMETHYLCARBINOL AND ITS COMPLEX ESTERS

M. A. Zakutskaya

The synthesis of trichlorinated carbinols with heterocyclic radicals and their complex esters has particularly interested investigators recently. 2-Furyl-, 5-methyl-2-furyl-, 2-thienyl, 5-chloro-2-thienyl, 2-pyrryl and N-methyl-2-pyrryltrichloromethylcarbinols are known at the present time [1-3]. The insecticide effect of these carbinols and their acetates was studied on mosquito larva, greenhouse aphids, house flies and citrus mites [3].

Howard [1] obtained 2-furyltrichloromethylcarbinol (I) from furfurol and chloroform by the action of caustic potash in 10.5% yield (on furfurol). Willard and Hamilton [2] using the same method synthesized (I) in 8.5% yield while from furan and sylvan with chloral in the presence of zinc chloride in glacial acetic acid they obtained 2-furyl- and 5-methyl-2-furyl-trichloromethylcarbinols. The yield of (I) was 44% (on chloral). Blinn [3] obtained a series of heterocyclic trichlorinated carbinols from organomagnesium compounds with chloral.

We studied the condensation of furfurol with chloroform under various conditions and synthesized a series of complex esters of 2-furyltrichloromethylcarbinol (II):



We used caustic potash, sodamide, anhydrous calcium oxide, as well as caustic potash with additions of anhydrous calcium oxide or sodium sulfate as condensing agents. The best results were obtained in the presence of caustic potash. We also studied the effect on condensation of the amount of chloroform and caustic potash, the time of KOH addition and temperature (table). The best yields of (I) (25%) were obtained in the reaction of 1 mole of furfurol with 4 moles of chloroform and 0.3 moles of KOH at room temperature. An increase in the amount of KOH to 0.5 moles lowered the yield of (I) while only traces of (I) were formed in the presence of 1 mole of KOH and the reaction proceeded almost wholly with the formation of α-furancarboxylic acid by the Canizzaro process. The latter was always found in the reaction products in greater or lesser amounts (up to 20% on furfurol). Up to 40% of the furfurol was recovered. The esters of 2-furyltrichloromethylcarbinol and fatty acids were obtained by the action of the corresponding anhydrides in a pyridine solution (yield 65-75%), while esters of benzoic, o- and p-chlorobenzoic acids were obtained by the action of the acid chlorides on the carbinol. The p-chlorobenzoate of the carbinol was most readily obtained and in the best yield. Ester crystals were rapidly formed (yield of 91.3%) by shaking mixtures of carbinol and p-chlorobenzoyl chloride with alkalis. The benzoate and o-chlorobenzoate of the carbinol were obtained less readily and in smaller yields. Shaking a mixture of the starting materials with alkali gave an oil, from which ester crystals were isolated by distillation in vacuum. The yield of benzoate was 32.5%, o-chlorobenzoate – 30.5%.

Synthesis of 2-Furyltrichloromethylcarbinol

Amount taken for reaction (in g)			Moles taken per 1 mole of furfurol		Reaction conditions			(I) obtained		Remarks
Furfurol	$CHCl_3$	KOH	$CHCl_3$	KOH	duration of addition (in hours)	temperature	stirring (in hours)	(in g)	(in %)	
50	50	10	0.8	0.36	1	0°	2	11	10.0	Experimental conditions according to Iotsich [4]
66	120	8	1.43	0.22	0.7	0	2.5	17	11.3	
66	120	8	1.43	0.22	1.5	20—25	1.5	18	12.2	Experimental conditions according to Willard [2]
33	90	4	2	0.22	1	0	2	8.5	11.5	
33	90	6	2	0.30	1	0	4	14	18.9	
66	170	12	2	0.30	2	0	4	26	17.3	
50	90	28	1.5	1.00	2	0	4	Traces	—	18 g of α-furancarboxylic acid was isolated
33	60	4	1.43	0.22	0.85	20—25	2.5	16.6	22.4	
33	90	6	2	0.30	1.5	20—25	3	16.5	22.4	
33	180	6	4	0.30	1.5	20—25	3	18.5	25.0	

EXPERIMENTAL*

Synthesis of 2-furyltrichloromethylcarbinol. Powdered caustic potash (6 g) was gradually added (1.5 hours) to a mixture of furfurol (33 g) and chloroform (180 g), which was stirred mechanically at room temperature. The mixture heated up noticeably, changed color from yellow to dark brown and formed a thick mass. After the addition of all the caustic potash, the thick mass was diluted with absolute ether (70 ml) and was stirred for a further 3 hours. Next day the precipitate of α-furancarboxylic acid salts was filtered off. After dissolving in water and acidifying, this yielded α-furancarboxylic acid with m.p. 128-130°. The ether and the chloroform were distilled off and the residue was distilled in vacuum. After distilling off the furfurol, we collected a fraction from 95-115° (5-8 mm), from which we isolated 2-furyltrichloromethylcarbinol as a colorless, oily liquid with b.p. 105-107° (5 mm), 112° (10 mm), 113-115° (13 mm). The yield was 18.5 g (25%). According to Howard [1] the b.p. is 115-118° (120 mm); presumably there was a printing error in reporting the pressure — 12 mm should have been written. Willard and Hamilton [2] reported b.p. 118-120° (12 mm) and 123-124° (15 mm).

d_4^{22} 1.5275, n_D^{22} 1.5319, MR_D 43.69; calc. 44.54. Found %: C 32.96; H 2.10; Cl 49.87. $C_6H_5O_2Cl_3$. Calculated %: C 33.37; H 2.10; Cl 49.39.

The acetate of 2-furyltrichloromethylcarbinol was a slightly yellow liquid with b.p. 110-115° (7 mm).

d_4^{25} 1.4065, n_D^{25} 1.5022, MR_D 54.03; calc. 53.91.

Synthesis of the propionate, n-butyrate and isovalerate of 2-furyltrichloromethylcarbinol. The esters were prepared similarly to the acetate of 2-furylchloromethylcarbinol [2,3]. Pyridine was added to a mixture of the carbinol and excess of the anhydride. The mixture heated up strongly and darkened. The mixture was left for 48 hours, then diluted with cold water, neutralized with solid potassium bicarbonate and extracted with chloroform. The chloroform solution was washed with dilute acetic acid, soda and water and dried over anhydrous sodium sulfate. After distilling off the chloroform, the residual oil was distilled in vacuum. The propionic, n-butyric and isovaleric esters of 2-furyltrichloromethylcarbinol were liquids with a specific aromatic smell.

Propionate. B.p. 143-145° (30 mm), d_4^{20} 1.3805, n_D^{20} 1.5015, MR_D 58.01; calc. 58.52.

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* R. Kh. Kolitsman and A. Z. Yunusov took part in the experimental part.

Found %: C 39.87; H 3.11; Cl 39.94. $C_9H_9O_3Cl_3$. Calculated %: C 39.78; H 3.33; Cl 39.22.

n-Butryate. B. p. 135-140° (15 mm), d_4^{20} 1.3332, n_D^{20} 1.5000, MR_D 62.98; calc. 63.14.

Found %: C 42.12; H 3.74; Cl 37.91. $C_{10}H_{11}O_3Cl_3$. Calculated %: C 42.03; H 3.88; Cl 37.25.

Isovalerate. B.p. 158-163° (35 mm), d_4^{20} 1.3027, n_D^{20} 1.4960, MR_D 67.20; calc. 67.76.

Found %: C 44.18; H 4.32; Cl 35.58. $C_{11}H_{13}O_3Cl_3$. Calc. %: C 44.08; H 4.37; Cl 35.50.

Synthesis of the benzoate and o- and p-chlorobenzoates of 2-furyltrichloromethylcarbinol. The esters were prepared by treating 2-furyltrichloromethylcarbinol (I) with the appropriate acid halide in the presence of 15% caustic soda, which was added until there was an alkaline reaction. The mixture was shaken till the separation of crystals, which were recrystallized from alcohol. If an oil separated instead of crystals, an ether extraction was carried out. The ether solution was dried and, after distilling off the ether, the residue was distilled in vacuum.

Benzoate. From 12.5 g of (I) we obtained 6 g (32.5%) of ester; m.p. 45° from alcohol.

Found %: C 48.56; H 2.80; Cl 33.18. $C_{13}H_9O_3Cl_3$. Calculated %: C 48.82; H 2.82; Cl 33.33.

o-Chlorobenzoate. From 10 g of (I) we obtained 5 g (30.5%) of ester; m.p. 37° (from alcohol).

Found %: C 44.23; H 2.43; Cl 40.10. $C_{13}H_8O_3Cl_4$. Calculated %: C 44.07; H 2.26; Cl 40.11.

p-Chlorobenzoate. From 7 g of (I) we obtained 10.5 g (91.3%) of ester; m.p. 57° from alcohol.

Found %: C 43.98; H 2.55; Cl 40.12. $C_{13}H_8O_3Cl_4$. Calculated %: C 44.07; H 2.26; Cl 40.11.

Laboratory tests showed that the propionate, benzoate and o- and p-chlorobenzoates of 2-furyltrichloromethylcarbinol were effective as soil treatments against the infection of verticilliose withering of cotton.

SUMMARY

1. 2-Furyltrichloromethylcarbinol was obtained in 25% yield from furfurol with chloroform in the presence of caustic potash.

2. The following complex esters of 2-furyltrichloromethylcarbinol were obtained for the first time: propionate, n-butyrate, isovalerate, benzoate, o- and p-chlorobenzoates.

LITERATURE CITED

[1] J. W. Howard, J. Am. Chem. Soc. 47, 455 (1925).

[2] J. R. Willard and C. S. Hamilton, J. Am. Chem. Soc. 73, 4805 (1951).

[3] R. C. Blinn, F. A. Gunther and R. L. Metcalf, J. Am. Chem. Soc. 76, 37 (1954).

[4] Zh. Iotsich, J. Russ. Chem. Soc. 29, 97 (1897).

Received October 27, 1955

Central Asian State University

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SUMMARY

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2. The following [illegible]

LITERATURE CITED

(1) [illegible] J. Am. Chem. Soc., [illegible]

(2) [illegible] and C. [illegible]

(3) [illegible] J. Am. Chem. Soc., [illegible]

(4) [illegible] J. Am. Chem. Soc., [illegible]

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THE OXONIUM COMPOUNDS OF COMPLEX ESTERS WITH ORGANIC ACIDS

IV. THE $CH_3COOC_4H_9-CCl_3COOH$, $CH_3COOC_5H_{11}-CCl_3COOH$ AND $CCl_3COOC_2H_5-CCl_3COOH$ SYSTEMS

M. Usanovich, K. Bilyalov and L. Krasnomolova

The complex esters were synthesized and purified, as described earlier [1]. The fractions of $CH_3COOC_4H_9$, $CH_3COOC_5H_{11}$ and $CCl_3COOC_2H_5$, boiling at 124° (682.2 mm), 132° (694.7 mm), 164° (691.1 mm) respectively, were isolated for this work. The trichloroacetic acid was fractionated several times; the fraction boiling at 187° (697.9 mm) was distilled into ampoules. The systems were studied at 50, 60 and 70° and their densities and viscosities were measured.

The $CH_3COOC_4H_9-CCl_3COOH$ system. The results of the measurements are given in Table 1.

TABLE 1

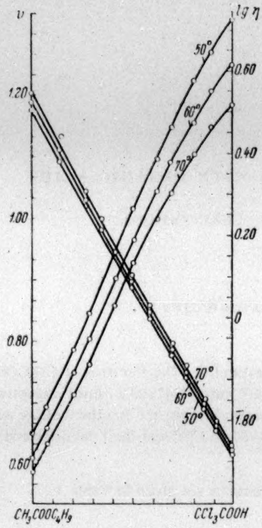
Ester content		Viscosity (in centipoises)			Density (in g/ml)		
(in mole %)	(in wt. %)	50°	60°	70°	50°	60°	70°
0.00	0.00	5.323	4.070	3.233	1.6156	1.6073	1.5905
10.40	7.60	4.361	3.495	2.870	1.5311	1.5155	1.5033
18.70	14.00	3.749	3.024	2.459	1.4492	1.4355	1.4202
30.13	23.40	2.85	2.351	1.978	1.3513	1.3371	1.3245
37.90	30.20	2.406	1.998	1.698	1.2845	1.2724	1.2582
49.40	40.90	1.798	1.515	1.302	1.1937	1.1810	1.1696
58.40	49.90	1.419	1.222	1.053	1.1267	1.1161	1.1048
71.06	64.60	0.996	0.866	0.750	1.0707	1.0207	1.0037
79.01	72.70	0.810	0.715	0.634	0.9803	0.9704	0.9575
92.90	85.70	0.588	0.526	0.479	0.8986	0.8802	0.8654
100.00	100.00	0.507	0.443	0.409	0.8503	0.8396	0.8292

Assuming that the values of the viscosity logarithms were additive, we plotted the viscosity diagrams on a semilogarithmic scale, as before [1-3]. The logarithmic viscosity isotherms (Fig. 1) pass through an inflexion point, which indicates reaction between the components. The specific volume diagram (Fig. 1) also indicates reaction (compression).

Thus, reaction occurs in the butyl acetate-trichloroacetic acid system. According to us this reaction occurs due to the hydrogen bond which forms between the hydrogen of the acid hydroxyl group and one of the oxygens of the complex ester.

The $CH_3COOC_5H_{11}-CCl_3COOH$ system. The investigation results are given in Table 2.

The logarithmic viscosity isotherms (Fig. 2) pass through an inflexion point, which indicates reaction. The specific volume diagram (Fig. 2) also indicates reaction. Thus, a hydrogen bond is formed in this system as in the previous case.



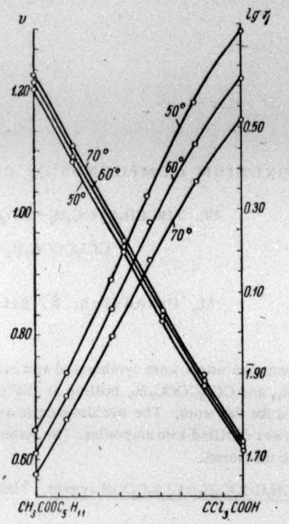


Fig. 1. Viscosity (composition in molecular percents) and specific volume (composition in weight percent) of the $CH_3COOC_4H_9-CCl_3COOH$ system.

Fig. 2. Viscosity (composition in molecular percents) and specific volume (composition in weight percent) of the $CH_3COOC_5H_{11}-CCl_3COOH$ system.

TABLE 2

Ester content		Viscosity (in centipoises)			Density (in g/ml)		
(in mole %)	(in wt. %)	50°	60°	70°	50°	60°	70°
0.00	0.00	5.323	4.070	3.233	1.6156	1.6073	1.5905
21.35	17.77	3.573	2.856	2.332	1.3934	1.3796	1.3657
43.25	37.77	2.146	1.838	1.504	1.2204	1.2097	1.1968
62.34	56.86	1.358	1.152	0.992	1.0743	1.0635	1.0514
84.21	81.11	0.807	0.710	0.623	0.9258	0.9158	0.9051
100.00	100.00	0.589	0.522	0.462	0.8363	0.8272	0.8177

TABLE 3

Ester content		Viscosity (in centipoises)			Density (in g/ml)		
(in mole %)	(in wt. %)	50°	60°	70°	50°	60°	70°
0.00	0.00	5.323	4.070	3.233	1.6156	1.6073	1.5905
23.58	26.56	3.172	2.599	2.164	1.5409	1.5275	1.5132
40.86	44.73	2.346	1.964	1.666	1.4870	1.4733	1.4590
59.88	63.62	1.742	1.493	1.291	1.4355	1.4213	1.4068
79.28	81.76	1.334	1.159	1.016	1.3880	1.3742	1.3609
100.00	100.00	1.037	0.915	0.803	1.3428	1.3294	1.3150

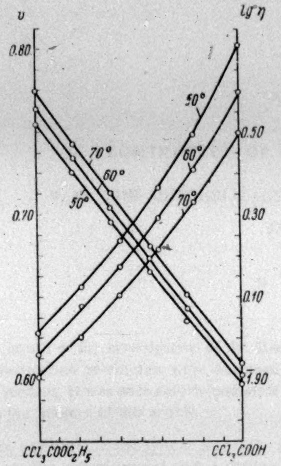


Fig. 3. Viscosity (composition in molecular percents) and specific volume (composition in weight percents) of the $CCl_3COOC_2H_5$ – CCl_3COOH system.

The $CCl_3COOC_2H_5-CCl_3COOH$ system. The results of the measurements are given in Table 3 and are shown graphically in Fig. 3.

The logarithmic viscosity diagram of this system (Fig. 3), in contrast to the previous two cases, does not indicate reaction directly. As the isotherms are convex toward the composition axis along the whole length, we presume that the reaction occurring in the system was hidden by the association of the trichloroacetic acid. The specific volume diagram shown in the same figure. is expressed by straight lines and may be explained by reciprocal compensation reactions which affect the specific volume in opposite directions.

SUMMARY

The viscosities and densities of the systems $CH_3COOC_4H_9-CCl_3COOH$, $CH_3COOC_5H_{11}-CCl_3COOH$ and $CCl_3COOC_2H_5-CCl_3COOH$ were studied at 50, 60 and 70°.

Reaction between components has been established for the first two systems. The presence of intermolecular reaction is presumed in the $CCl_3COOC_2H_5-CCl_3COOH$ system although it was not reflected in the diagrams.

LITERATURE CITED

[1] M. Usanovich, K. Bilyalov and L. Krasnomolova, J. Gen. Chem. 25, 471 (1955).

[2] T. N. Sumarokova and K. Bilyalov, J. Gen. Chem. 25, 477 (1955) (T.p. 439).[*]

[3] M. Usanovich, K. Bilyalov and L. Krasnomolova, J. Gen. Chem. 26, 1881 (1956).

Received November 14, 1955

Institute of Chemistry of the Academy of Sciences of the Kazakh SSR

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[*] T. p = C. B. Translation pagination.

BROMINATION OF UNSATURATED COMPOUNDS

V. BROMINE ADDITION REACTIONS OF ALLYLTRIMETHYLAMMONIUM PERCHLORATE

N. P. Kanyaev

The results of the investigation of the kinetics of hypobromous acid addition at the double bond of allyltrimethylammonium perchlorate were described in a previous report [1]. As hypobromous acid is a bromine hydrolysis product, it was necessary to complete the existing data by investigating the kinetics of bromine addition and this is the subject of this article.

Some equilibria in the system Br_2-H_2O. In an aqueous solution active bromine may be in various forms which are readily interconverted with a change in the pH of the medium and the bromine ion concentration. We will examine only those of them which are of interest to us. The Equilibria 1-4 determine the state of the brominating agents:

$$Br_2 + H_2O \rightleftarrows HOBr + H^+ + Br^-; \quad K_1[Br_2] = [HOBr][H^+][Br^-]. \tag{1}$$

In Liebhafsky's latest paper [2] the value $0.69 \cdot 10^{-9}$ is given for K_1 at 0°. Calculations for 0.005 M bromine water, used in this investigation, show that 8% of the bromine hydrolyzes.

$$Br_2 + Br^- \rightleftarrows Br_3^-; \quad K_2[Br_3^-] = [Br_2][Br^-]. \tag{2}$$

Using the equation $\log K_2 = -\frac{340}{T} - 0.09$ to determine the value of K_2, Liebhafsky obtained a value equal to 0.0462 at 0°. From this value it is possible to calculate that at a concentration of $Br_2 = 0.005$ and $Br^- = 0.1\,M$ 68% of the bromine is converted into the tribromide ion. Conversion of the bromine into the pentabromide ion is not considered as its concentration is very small according to calculations.

$$Br_2 \rightleftarrows Br^+ + Br^-; \quad K_3[Br_2] = [Br^+][Br^-]. \tag{3}$$

Presumably, the most reliable value for K_3 at 25° is $\sim 10^{-20}$ as given in the paper by Bell and Gelles [3] who consider that free halogen cations do not exist but may occur in an aqueous solution as the hydrates. They were able to confirm experimentally the theoretically calculated value of the analogous constant for iodine.

$$Br^+ + H_2O \rightleftarrows HOBr + H^+; \quad K_4[Br^+] = [HOBr][H^+]. \tag{4}$$

Constant K_4 is found by combination of (1) and (3). Its value is $K_4 = \frac{K_1}{K_3} = 7 \cdot 10^{10}$.

EXPERIMENTAL

Notation used: allyltrimethylammonium perchlorate is now denoted everywhere by AA; a and b are concentrations of AA and Br_2 respectively, expressed in milliliters of 0.01 N thiosulfate; a_0 and b_0 are the same values at the beginning of the reaction; t is the time from the beginning of the reaction in minutes; k_2 is the experimental constant of the second order, calculated by the formula $k_2 = \frac{460.5}{t(a_0 - b_0)} \cdot \log \frac{a \cdot b_0}{a_0 \cdot b}$; the reagent formulae in square brackets denote the actual concentrations, in round ones, the analytical concentrations (moles/liter); the dimensions of the rate constants are $\text{moles}^{-1}/\text{liters} \cdot \text{minutes}^{-1}$; the temperature of the experiments was 0° (unless another value is given).

Products of the reaction of AA with bromine. Treatment of AA with a dilute solution of bromine yielded almost entirely the hydroxybromo-derivative, the same as in the addition of HOBr. This was shown by the appearance of an almost equivalent quantity of HBr. Treatment with bromine in the presence of bromide ions gave the hydroxybromo-derivative and the dibromo derivative. The direction of the reaction in the presence of nitrate, bromide, chloride and mercuric chloride is given in Table 1.

TABLE 1

Concentration of bromine (in g mol/liter)	Name and concentration of additive (in g mol//liter)		Yield of hydroxyhalogeno derivative (in %)
0.00642	$[KNO_3]$	0.1	94
0.00624	[KBr]	0.05	75
0.00571	[KBr]	0.20	43
0.00546	$[KNO_3]$	0.2	94
0.00546	[KCl]	0.05	89
0.00521	[KCl]	0.20	83
0.00579	$[HgCl_2]$	0.0008	100

From the data in Table 1, it is obvious that the bromide ion is more effective than the chloride ion in changing the direction of the reaction toward the formation of the dibromo derivative. From experiments with 0.05 M KBr and KCl it may be estimated that the bromide ion is approximately 5 times as active as the chloride ion.

In the presence of mercuric chloride, only the hydroxybromo derivative was formed due to the bromide ion being bound up in complexes. The direction of the reaction is slightly dependent on the concentration of bromine.

Two experiments on the reaction of AA with bromine are given in Table 2 as an example.

TABLE 2

$[AA] = 0.0245$, $[Br_2] = 0.0100$			$[AA] = 0.0514$, $[Br_2] = 0.00234$		
t	b	k_2	t	b	k_2
0	2.003	—	0	0.469	—
8	1.497	1.58	8	0.248	1.58
15	1.207	1.53	12	0.185	1.53
40	0.632	1.43	18	0.121	1.49
70	0.329	1.38	25	0.075	1.45
Average		1.46	Average . .		1.51

The rate coefficients of the reaction of AA with bromine decrease slightly with an increase in the reaction time. This shows that the bromine does not appear in the kinetic equation in the first but in a slightly higher power. However, the change in the initial concentrations of the reagents hardly alters the value of the bimolecular rate constant and therefore, in the first approximation, the most appropriate kinetic equation for this reaction appears as:

$$-\frac{d[Br_2]}{dt} = k_2[AA][Br_2]. \quad (I)$$

The introduction of bromide ion into the reaction mixture lowers the rate of reaction of AA with bromine and the introduction of nitrate ion slightly increases it. In both cases the rate constants become more constant. The results of these experiments are given in Table 3.

The retarding effect of the bromide ion is explained by the reduction in the concentration of bromine due to its conversion to Br_3^-, which adds to a double bond more slowly. The change in the initial bromine concentration in this case does not alter the experimental constant k_2 and the most suitable kinetic equation is:

$$-\frac{d(\mathrm{Br_2})}{dt}=k'[\mathrm{AA}][\mathrm{Br_2}]+k''[\mathrm{AA}][\mathrm{Br_3^-}]. \qquad \text{(II)}$$

TABLE 3

The Effect of NO_3^- and Br^- on the Addition of Br_2 to AA

[AA]	(Br_2)	NO_3^-	Br^-	k_2	k'	k''
0.0244	0.00498	0.050	—	1.60	1.60	—
0.0244	0.00498	—	0.050	1.12	1.60	0.66
0.0244	0.00523	0.100	—	1.75	1.75	—
0.0244	0.00523	—	0.100	0.99	1.75	0.64
0.0255	0.00432	0.100	0.100	1.09	2.03	0.66
0.0255	0.00432	0.100	0.100	1.09	2.03	0.66
0.0255	0.00432	0.200	—	2.03	2.03	—
0.0255	0.00432	—	0.200	0.87	2.03	0.60

TABLE 4

Name and concentration of additive (in g mole/liter)	0°	20°	φ	(in cal)	α
	k_2				
Нет	1.57	11.4	2.7	16000	$1.0 \cdot 10^{11}$
$[NaNO_3]$, 0.200 . . .	2.03	15.3	2.8	16000	$3.3 \cdot 10^{11}$
	k''				
[NaBr] 0.200 . . .	0.60	4.61	2.8	16000	$9.7 \cdot 10^{10}$
$[NaNO_3]$ 0.100 [NaBr] 0.100 . . .	0.66	4.75	2.7	16000	$4.0 \cdot 10^{10}$

Using Equation (2), it is possible to establish that the experimental rate coefficient is of the second order:

$$k_2=\frac{K_2\cdot k'+k''[\mathrm{Br}^-]}{K_2+[\mathrm{Br}^-]}.$$

Assuming that $k' = k_2$ for experiments without bromide, but with the same concentration of potassium nitrate, added to eliminate salt effects, we can determine k'', whose values are given in Table 3.

The effect of temperature. Experiments were carried out at 0 and 20°. The experimental data and the calculated values of the temperature coefficient φ, the activation energy Q and the factor before the exponential α are given in Table 4. For experiments in the presence of bromide, the calculations were carried out allowing for the rate coefficients of the reaction of AA with Br_3^- (k'').

DISCUSSION OF RESULTS

The reaction of bromine with AA in an aqueous solution is expressed approximately by an equation of the second order. However, water participates in the reaction and, consequently, the transition complex is composed of three molecules. As a triple collision is not very probable, the reaction occurs in two stages: it starts with an attack by the bromine molecule, which draws into its sphere of action the double bond π-electrons, then in the second stage, a water molecule, which is an electron donor, is attracted by the positively polarized carbon and the active complex decomposes with the formation of bromohydrin and hydrogen bromide. Apparently, the attacking bromine molecule is not polarized and the polarization process is completed in the transition complex. This conclusion was arrived at on the basis of the enormous difference in the reactivity of a bromo-cation [1] and a bromine atom. The large hydration energy of the ions, especially that of the protons, strongly promotes reaction in an aqueous medium.

The hypobromous acid found in the bromine water, contrary to strongly accepted opinion [4], does not play a noticeable part in the formation of the bromohydrin, the main reaction product, as the HOBr concentration is very small and, furthermore, its rate of reaction with AA is approximately 50 times less than the rate of AA reaction with bromine. The view that the hydrogen ion makes HOBr many times more active than bromine is untenable here for if it is assumed that HOBr participates in the reaction, then the kinetic equation appears as:

$$-\frac{d[Br_2]}{dt} = k'[AA][Br_2] + k[AA][HOBr][H^+]$$

and, expressing [HOBr] in terms of [Br_2], it may be deduced that the experimental magnitude of $k_2 = k' + k\frac{K_1}{[Br^-]}$ must not depend on [H^+]. In this way, the conditions of Equilibrium (1) disprove the assumption that the hydrogen-ion has an activating capacity. The addition of nitric acid hardly changes the reaction rate and this proves that hydrogen-ion does not activiate AA and Br_2.

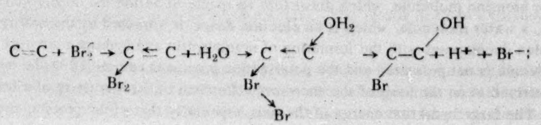
Buffer solutions, which greatly accelerate reaction with HOBr, slightly increase the rate of addition in the case of the Br_2 reaction. Probably, active brominating agents of the type BrA (for example $BrOOCCH_3$) form less readily in the latter case than in the presence of hypobromous acid. Pyridine slows down the reaction very strongly while pyridine-nitrate slows it down a little less. There is a paper in the literature which recommends pyridine as a bromination catalyst [5,6]. Obviously, this report is incorrect, as the same brominating agents take part in substitution in an aromatic compound as in addition at a double bond.

The introduction of mercuric chloride has a strongly catalytic effect. Mercurous and mercuric nitrates have a weaker action. This effect of mercury salts depends greatly on bromide ion additions which destroy their catalytic action. The catalytic action of mercury salts was noted in the nitration and sulfonation of aromatic compounds [7] and it was proved that it occurred through the formation of mercurated products [8]. The analysis of AA bromination experiments indicated a different mechanism: mercury salts, bonding the bromide ion in a complex, cause the formation of extremely powerful brominating agents – a bromo-cation and bromo-chlorine (in the presence of mercuric chloride). As HBr is formed during the reaction, the effect of the addition of bromide ion was studied. Here, the effect of two brominating agents – Br_2 and Br_3^- – and the formation of two reaction products – bromohydrin and dibromide – have to be considered. Therefore, the kinetic Equation (II) has to be rewritten as:

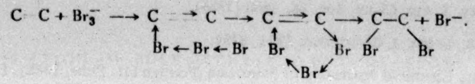
$$\frac{d(Br_2)}{dt} = k'[AA][Br_2] + l[AA][Br_3^-] + l'[AA][Br_3^-]. \tag{III}$$

Equations (III) and (II) are indistinguishable from the kinetic point of view. It is assumed that the overall bromination rate in Equation (III) consists of three rates: the first (first term of the sum of the rates) is the rate of bromohydrin formation by the action of bromine and water, the second is the rate of formation of bromohydrin and, possibly, a small amount of dibromide by the action of Br_3^- and H_2O and the third is the rate of dibromide formation as a result of the action of the tribromide ion.

According to existing experimental material, which will be described later, the tribomide ion may have a dual nature, that is, it can be an electrophilic reagent (electron acceptor) and due to its action hydroxybromide and dibromide may be formed, but at the same time, it is a nucleophilic reagent (electron donor) by which only dibromide may be formed. Nucleophilic Br_3^- is excluded from the process in the double bond region of various unsaturated compounds with a large electron density. However, with a decrease in the reactivity of the double bond, it makes its appearance and plays an increasingly greater role in the formation of reaction products. In the reaction of bromine with AA it is already significant. In the light of present day theory [9] the hypothetical reaction mechanism of bromohydrin formation may be expressed in the following way:



The tribromide ion, which includes both donor and acceptor groups, reacts in the second course of the reaction according to an analogous scheme, by attacking the double bond through its acceptor part. Dibromide formation proceeds in a different way in the third course. Tribromide ion acts as an electron donor and reacts according to the scheme:



Thus, the reaction of hypobromous acid [1] and bromine with AA proceeds by using the most reactive forms of the brominating agent. The bimolecular rate coefficients for the various brominating agents are compared in Table 5.

Hypobromous acid probably acts mainly by means of the bromo-cation as the water for the solutions was not protected from atmospheric carbon dioxide and the addition of the smallest amounts of alkali considerably lowered its addition rate.

The bimolecular rate constants cannot be calculated for reagents of the BrA type (except for BrCl) due to the absence of appropriate equilibrium constants, but the rate of their action on AA is greater than that of bromine.

TABLE 5

The Values of the Bimolecular Constants for Brominating Agents.

Agent	$H_2O\overset{+}{B}r$	BrCl	Br_2	Br_3^-	HOBr
k	$2 \cdot 10^{14}$	5700	1.60	0.65	0.025

On the basis of experimental data, we can arrange the brominating agents in a series according to their activity:

$$H_2O\overset{+}{B}r \gg BrCl \text{ и } BrA \gg Br_2 > Br_3^- > HOBr.$$

The bimolecular constants for chlorination of AA by chlorine are known from the literature [10], and they show that chlorine is approximately 25 times more active than bromine.

SUMMARY

1. Addition of bromine to allytrimethylammonium perchlorate proceeds by a reaction of the second order. An hydroxybromide compound is the main reaction product, although hypobromous acid does not play a significant part in the process.

2. Mercuric chloride is an effective reaction catalyst, due to its capacity of facilitating bromo-cation and bromo-chlorine formation in the bromine solution. With it, there is an increase in the amount of bromohydrin formed.

3. The introduction of bromide ion slows down the reaction. This is explained by the conversion of part of the bromine into tribromide ion, whose reactivity is approximately 2.4 times less than that of bromine.

4. Brominating agents of allyltrimethylammonium perchlorate in an aqueous solution are given together with approximate values for their relative reactivity.

LITERATURE CITED

[1] N. Kanyaev, J. Gen. Chem. Suppl. II, 1171 (1953).

[2] H. Liebhafsky, J. Am. Chem. Soc. 56, 1500 (1934).

[3] R. Bell and E. Gelles, J. Chem. Soc. 1951, 2734.

[4] R. Goldshtein, Chemical Processing of Petroleum (Foreign Lit. Press, 1952), 171.

[5] W. Cross and J. Cohen, Proc. Chem. Soc. 24, 15 (1908).

[6] L. Ortner, L. Reikhel, Practical Handbook of Organic Chemistry, State Chem. Tech. Press, 1932, 33.

[7] N. Vorozhtsov, The Foundations of the Synthesis of Intermediary Products and Dyes (State Chem. Press, 1950), 92, 141.

[8] A. Titov and N. Laptev, J. Gen. Chem. 19, 267 (1949).

[9] E. Shilov, Problems on Chemical Kinetics, Catalysis and Reactivity (Acad. Sci. USSR Press, 1955), 749.

[10] E. Shilov, G. Kupinskaya and A. Yasnikov, Proc. Acad. Sci. USSR 81, 437 (1951).

Received November 23, 1955

Ivanovsky Institute of Chemical Technology

ISOMERIZATION OF POLYMETHYLENE HYDROCARBONS BY ALUMINUM CHLORIDE

XIX. ISOMERIZATION OF 1,3,5-n-TRIMETHYLCYCLOHEXANE AND ISOPROPYLCYCLOHEXANE

M. V. Turova-Polyak, Z. S. Kraits and E. G. Treshchova

In a previous paper [1] it was shown that the action of aluminum chloride on cyclohexane homologs of the general formula C_8H_{16} (1,1-dimethylcyclohexane, 1,2-dimethylcyclohexane and ethylcyclohexane) consisted of a transference and disproportionation of radicals. In each case a mixture of hydrocarbons was obtained with approximately the same composition (58% 1,3-dimethylcyclohexane, 20% 1,4-dimethylcyclohexane, 14% 1,2-dimethylcyclohexane and 6% 1,1-dimethylcyclohexane), which invariably contained 1,1-dimethylcyclohexane. There was no isomerization of the hydrocarbon ring.

The action of aluminum chloride on cyclohexane homologs of the general formula C_9H_{18} has been little studied. As the conditions under which the reaction was carried out by various investigators differed, the results they obtained, therefore, often contradicted each other [2].

We considered it of interest to develop our investigations and study the effect of aluminum chloride on this class of hydrocarbons, and, specifically, on 1,3,5-trimethylcyclohexane,* and n- and isopropylcyclohexane, under the conditions we had set before, and to find out if the conclusions arrived at in the previous work [1] would also hold for the cyclohexane homologs of the general formula C_9H_{18}. This problem also interested us as we had previously shown that butylcyclopentane [4] and ethylcycloheptane [5] were isomerized by aluminum chloride mainly into trimethylcyclohexanes.

The experiments in this work were carried out under conditions simillar to those for butylcyclopentane and ethylcyclopheptane isomerization, that is at 100° and at the boiling points of the hydrocarbons . Some experiments were also carried out at 0 and at 25°.

Optical analysis using combination light scattering was used for finding the composition of the reaction products. The reaction products obtained in experiments carried out at 100° and at the boiling points of the hydrocarbons differed in their constants from the original hydrocarbons but were similar to each other. The boiling point varied within the range 134-142°, the refractive index at 20° varied from 1.4270 to 1.4286 and specific gravity at 20° varied from 0.7752 to 0.7760.

The spectra of the isomerization products of normal and isopropylcyclohexane, obtained in experiments carried out at 100° and the boiling points of the hydrocarbons, were similar to each other, but differed somewhat from the spectra of isomerization products of 1,3,5-trimethylcyclohexane obtained under analogous conditions.

We considered that, beside the original hydrocarbons, mixtures of various trimethylcyclohexane isomers were present in the reaction products. However, there is no reference at the present time on the spectra of many of them (specifically, cis-trans-isomers of 1,2,3- and 1,2,4-trimethylcyclohexanes).

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* In 1941 one of us [3] studied the reaction of aluminum chloride with 1,3,5-trimethylcyclohexane; at that time we used a dehydrogenating catalyst for investigating the reaction products. We considered it would be of interest to repeat this work using the combination light scattering method so as to obtain results that could be compared with those obtained by isomerization of propylcyclohexanes.

We used the data obtained by Bazhulin [6] and Chiurdoglu [7] on the individual trimethylcyclohexanes and isomer mixtures, for calculating the quantitative composition of the isomerization products of 1,3,5-trimethylcyclohexane and n- and isopropylcyclohexane.

The 1,3,5-trimethylcyclohexane content was determined by the lines at 840 and 520, 1,2,4-trimethylcyclohexane – by the line at 747, 1,1,3-trimethylcyclohexane – by the line at 726 and the 1,1,4-trimethylcyclohexane content was determined by the line at 705.

A rather intense line at 499 cm^{-1} was also present in the spectra of isomerization products, obtained under the above conditions. However, this line could not be assigned to a particular isomeric trimethylcyclohexane on the basis of the existing literature data. According to Chiurdoglu's data [7] this line is absent from the 1,3,5-trimethylcyclohexane spectrum,[but it is present as a low intensity line at 502 [1] in the 1,2,3-trimethylcyclohexane spectrum]and as a line at 497 [1] in the 1,2,4-trimethylcyclohexane spectrum.

In the spectra of the hydrocarbon mixtures that we investigated, the lines of 1,2,3-trimethylcyclohexane were 7 – 8 times more intense than the 499 cm^{-1} line and, therefore, this line could not be assigned to 1,2,3-trimethylcyclohexane. Nor can this line be assigned to 1,2,4-trimethylcyclohexane as other, much more intense, lines of this hydrocarbon have an intensity in our spectrum close to that of the 499 cm^{-1} line.

Due to this, we were forced to ignore the 499 cm^{-1} line and other weaker spectrum lines in carrying out calculations. The line at 499 cm^{-1} possibly belongs to trimethylcyclohexane isomers that have not yet been investigated spectroscopically; therefore, the composition of the isomerization products has an approximate character. Lines, characterizing other rings, were not found in the reaction products.

As a result of the isomerization of n- and isopropylcyclohexanes at 100° and at their boiling points, a hydrocarbon mixture was obtained consisting of approximately 18% 1,1,3-trimethylcyclohexane, 37% 1,1,4-trimethylcyclohexane, 27% 1,2,4-trimethylcyclohexane and 18% 1,3,5-trimethylcyclohexane.

In carrying out the reaction with 1,3,5-trimethylcyclohexane under the above conditions, 25-30% of it remained unchanged, while its isomerization products consisted of 20-23% 1,1,3-trimethylcyclohexane, 15-17% 1,1,4-trimethylcylohexane and 35% 1,2,4-trimethylcyclohexane.

The reaction products obtained by the reaction of 1,3,5-trimethylcyclohexane, n- and isopropylcyclohexane with aluminum chloride at 0°, practically did not differ from the original hydrocarbons either in constants or spectra.

Similiar results were obtained in the reaction with 1,3,5-trimethylcyclohexane and n-propylcyclohexane at 25°.

Thus, the results of the experiments carried out show that the action of aluminum chloride on the cyclohexane homologs of the general formula C_9H_{18} consisted, as in the case of hydrocarbons of the formula C_8H_{16}, of only the transference and disproportionation of radicals and that the 1,3,5-trimethylcyclohexane system was the most stable. There is no ring isomerization in this case either. A considerable amount of hydrocarbons (about 50%) with two methyl groups in the gem-position is characteristic of the equilibrium mixture as in isomerization of C_8H_{16} hydrocarbons. These observations are interesting in connection with the fact that hydrocarbons with similiar structure are invariably found in investigations of the individual composition of the benzenes.

EXPERIMENTAL

Synthesis of starting hydrocarbons. 1,3,5-Trimethylcyclohexane was prepared by hydrogenating commercial mesitylene over Raney nickel at 180-200° and 100-120 atm. The constants and the spectrum of the 1,3,5-trimethylcyclohexane we obtained and the constants of this hydrocarbon according to literature data are given in Table 1.

The spectrum of the 1,3,5-trimethylcyclohexane, which we prepared, coincided almost completely with the spectra given by P. A. Bazhulin [6] and Chiurdoglu [9] for a mixture of geometric isomers of 1,3,5-trimethylcyclohexane.

Spectrum: 254(3), 310(0.5), 325(0.1), 365(0), 408(8), 413(0.5), 434(10), 460 (0.5 broad), 510 (0), 518(15), 621(0), 635(1.5), 787(1.5), 831(0.3), 845(6.5), 943(0.5 broad), 970(0.5), 1000(1.5), 1022(1), 1046(6.5), 1070(1.5), 1095(1.5 broad), 1117(1), 1144(0.5) 1174(25 fundamental), 1255 (0.3), 1267 (1.5), 1270 (0.3), 1303(0.1); 1328(0.2), 1342(6), 1354(1), 1358(0.5), 1408(0 broad), 1439 (1.8), 1462(10).

TABLE 1

1,3,5-Trimethylcyclohexane	Boiling point	n_D^{20}	d_4^{20}	MR_D		Literature reference
				Found	Calculated	
Mixture of isomers	138.5—140° (743 mm)	1.4270	0.7722	41.86	41.56	Prepared in the present work
	138.5—140° (760mm)	1.4272	0.7713	—	—	[9]
	137.8—139° (747mm)	1.4280	0.7700	—	—	[6]
Trans form	140.55° (760 mm)	1.4310	0.7789	—	—	[7]
Cis form	138.55° (760 mm)	1.4268	0.7705	—	—	[7]

n-Propylcyclohexane was synthesized from n-propyl bromide and cyclohexanone. The n-propylcyclohexanol, prepared by the Grignard reaction, was dehydrated with anhydrous aluminum sulfate by the method described by Signaigo [8]. The n-propylcyclohexene was hydrogenated to n-propylcyclohexane in the vapor phase at 170-180° using a partially alkali-extracted alloy of nickel and aluminum [10]. The catalyst was prepared in the following way: fine pieces of the alloy, which contained 40% nickel, were placed in a procelain basin and 10% sodium hydroxide solution was added in small portions at such a rate that the temperature of the reaction mixture did not exceed 20-25°. Sufficient alkali was used to dissolve about 10% of the aluminum. The preparation of the catalyst was completed by heating the reaction mixture on a water bath at 60° for 1.5 hours. After this the catalyst was washed with water till a neutral reaction to phenolphthalein and it was placed wet in the catalyst tube, through which nitrogen was passed for 1 hour in the cold and then hydrogen for a further hour. After this the hydrogen flow was continued while the temperature of the furnace was slowly raised to 160-180° and maintained at this level until all the moisture had been removed. The catalyst prepared in this way had a high activity. A single passage of benzene at a volume rate of 0.25 yielded cyclohexane with n_D^{20} 1.4263.

After suitable purification, the n-propylcyclohexane prepared over this catalyst was distilled over metallic sodium.

The constants and spectrum are given in Table 2.

TABLE 2

Boiling point	n_D^{20}	d_4^{20}	MR_D		Literature reference
			Found	Calculated	
154.6—155.6° (752 mm)	1.4370	0.7933	41.58	41.56	Prepared in this work
154.9—155° (760 mm)	1.4370	0.7930 (d_{20}^{20})	—	—	[8]
156.5° (760 mm)	1.4368	0.7932	—	—	[7]

Spectrum: 182 (0.3), 193 (0.5), 224 (0.2), 242 (1), 276 (0), 299 (4), 329 (0.2), 357 (0.1), 387 (0.2), 401 (0.1), 434 (0.2), 445 (3), 460 (0), 544 (0.3), 567 (0.5), 603 (0.1), 678 (0), 697 (0), 733 (0.1), 738 (1), 750 (0), 769 (0.8) 784 (5 broad), 794 (1), 845 (2), 868 (0.8), 875 (1), 897 (1), 928 (0.2), 956 (0.2), 972 (0.6), 1037 (8), 1054 (1), 1080 (1), 1085 (2), 1102 (1.5), 1157 (1), 1166 (2 broad), 1192 (1.3), 1204 (0.2), 1255 (1), 1267 (2), 1270 (1.5), 1296 (1.5), 1314 (0.2), 1346 (1.5), 1357 (1), 1382 (0.6), 1443 (10), 1460 (10).

According to the spectrum analysis data, the n-propylcyclohexane we obtained, contained 97-98% of normal and 2-3% of isopropylcyclohexane.

Isopropylcyclohexane was prepared by hydrogenating commercial isopropylbenzene over Raney nickel at 180-200° and 100-120 atm of hydrogen. After suitable purification, the isopropylcyclohexane obtained was distilled over metallic sodium.

The constants and spectrum are given in Table 3.

TABLE 3

Boiling point	n_D^{20}	d_4^{20}	MR_D Found	MR_D Calculated	Literature reference
153.8—154.2° (753 mm)	1.4402	0.8004	41.52	41.56	Prepared in this work
151.7—153.0° (760 mm)	1.4411	0.7992 (d_{20}^{20})	—	—	[8]
154.5° (760 mm)	1.4409	0.8022	—	—	[11]
154.8° (760 mm)	1.4411	0.8018	—	—	[7]

Spectrum of isopropylcyclohexane: 218 (0.4), 247 (0.5), 291 (0.8), 311 (2.5 broad), 335 (2), 373 (0.3), 413 (1 broad), 441 (2), 464 (2), 494 (2), 530 (1), 570 (2), 706 (0.5), 769 (4.5), 785 (1.2), 822 (1.8), 858 (2), 884 (0.5), 927 (0.3), 956 (2.5 broad), 986 (0.5), 1038 (11 broad), 1085 (2.5), 1117 (1), 1164 (3 broad), 1192 (2), 1241 (1), 1267 (3.5), 1296 (1.8), 1319 (0.3), 1341 (1 broad), 1350 (0.5), 1382 (0.3), 1443 (10), 1463 (1.5).

According to the spectrum analysis data, the isopropylcyclohexane we obtained, contained 88% iso- and 12% n-propylcyclohexane.

Isomerization of 1, 3, 5-trimethylcyclohexane and isopropylcyclohexane. The isomerization of both these hydrocarbons was carried out in the apparatus that we used in previous work, for 20 hours at 0, 25 and 100° and at the boiling point of the hydrocarbons. The molar ratio of aluminum chloride and hydrocarbon was the same in all cases and equalled 1 : 3. The hydrocarbons were distilled over metallic sodium immediately before the reactions and the aluminum chloride was sublimed.

At the end of the experiments, the reaction products were separated from the aluminum chloride, washed carefully and distilled over metallic sodium. Even distillation on efficient columns was not worth while as the isomerization products were complex mixtures of hydrocarbons with very close boiling points.

The combination scattering spectra were determined on a three prism Steichel spectrograph. The apparatus and the method of plotting, interpreting and calculating are described in a paper by one of us [12].

The experiments at 0° were carried out in the following way. Aluminum chloride was added to the hydrocarbons cooled to 0°. This did not produce a rise in temperature. The experiments were carried out for 20 hours with continuous mechanical stirring.

At the end of the reaction, the aluminum chloride had not changed externally.

The constants of the reaction products, after suitable purification and distillation, were practically the same as the constants of the starting hydrocarbons (Table 4).

At 25°, the reaction was carried out only with 1, 3, 5-trimethylcyclohexane and n-propylcyclohexane. Also in this case, at the end of the reaction the aluminum chloride had not changed externally and no significant change in the constants of the reaction products was observed (Table 4).

In carrying out the experiments at 100°, the reaction mixture was heated on an oil bath (the temperature of the oil was 102-103°). After 7-8 hours of reaction, the aluminum chloride began to change and gradually turned into a viscous mass. In Table 4 we give the constants of the isomerization products and their compositions according to the spectrum analysis data.

Below we give the spectra of these products.

Spectrum of the products of isomerization of 1,3,5-trimethylcyclohexane: 253(1.2), 257(0.5), 285(0.5), 326(1.5), 348(0.1), 369(0.8), 384(0.1), 397(1), 406(1.3 broad), 434(1.5), 441(1), 460(1.8), 474(0.5), 499(2.2), 518(2.5), 539(0), 556(1.5), 586(0.3), 673(0.1), 704(1.5), 726(2), 748(3), 787(0.6 broad), 831(0.5), 845(1.6), 912(0.5), 950(1 broad), 965(0.1), 998(0.5), 1046(2) 1070(1.5), 1082(1.5), 1096(1), 1144(0.2), 1167(2), 1180(3), 1193(2), 1219(0.5), 1241(0.5), 1267(2), 1305(0.5), 1345(2), 1353(3), 1408(0.5), 1440(2), 1459(10).

TABLE 4

Starting hydrocarbons	Constants of starting hydrocarbons	Constants and composition of isomerizates at			
		0°	25°	100°	boiling point of hydrocarbons
1,3,5-trimethylcyclohexane					
B.p.	138.5-140°	138-140°	139-140.4°	136.5-143°	136.5-143°
n_D^{20}	1.4270	1.4270	1.4275	1.4274	1.4274
d_4^{20}	0.7722	0.7719	0.7729	0.7755	0.7752
Yield of isomerization products (in %)	–	95	88	85	90
Composition of isomerization products	–	Unchanged 1,3,5-trimethylcyclohexanes		Trimethylcyclohexane	
				1,1,3-23% 1,1,4-17 1,2,4-35 1,3,5-25	1,1,3-20% 1,1,4-15 1,2,4-35 1,3,5-30
n-Propylcyclohexane					
B.p.	154.6-155.6°	154-155.5°	153-156°	135-142°	135.5-143°
n_D^{20}	1.4370	1.4370	1.4365	1.4290	1.4290
d_4^{20}	0.7933	0.7930	0.7936	0.7764	0.7766
Yield of isomerization products (in %)	–	94	85	88	85
Composition of isomerization products	Unchanged n-propylcyclohexane			Trimethylcyclohexanes 1,1,3-18% 1,1,4-37 1,2,4-27 1,3,5-18	
Isopropylcyclohexane					
B.p.	153.8-154°	153.8-154°	–	134.5-141.5°	133.7-143°
n_D^{20}	1.4402	1.4400	–	1.4287	1.4286
d_4^{20}	0.8002	0.8004	–	0.7760	0.7764
Yield of isomerization products (in %)	–	95	–	90	88
Composition of isomerization products	–	Unchanged isopropylcyclohexane	–	Trimethylcyclohexanes 1,1,3-18% 1,1,4-37 1,2,4-27 1,3,5-18	

Spectrum of the products of isomerization of n- and isopropylcyclohexane: 170(0.5), 253(2), 264(0.5), 299(0.1), 325(2), 347(0.2), 365(0.8), 380(0.3), 397(1.8), 408(2 broad), 434(1.8), 446(1.5), 460(1.5), 499(3), 518(3.5), 538(0.3), 556(2), 582(0.1), 702(1.5), 726(2), 748(4), 775(0.2), 787(1), 795(0.2), 833(0.8), 845(1.5), 868(0.1), 918(0.8), 938(0.5), 950(2), 972(0.9), 985(0.8), 1001(1), 1046(2.5), 1068(1), 1083(1.8), 1100(1.5), 1120(0.3), 1166(2), 1175(4), 1190(2), 1219(0.8), 1231(0.5), 1253(0.5), 1268(0.5), 1317(1), 1323(0.3), 1341(2), 1352(2.5), 1380(0.5), 1408(0.5), 1433(2), 1460(10).

The experiments at the boiling points of the hydrocarbons were carried out at 138-140° for 1,3,5-trimethylcyclohexane and at 150-155° for n- and isopropylcyclohexane. After 4-5 hours, the aluminum chloride began to change into a viscous mass and after 9-10 hours it was converted into a brownish red, syrupy liquid. In Table 4 we give the constants of the isomerization products and their compositions according to spectrum analysis data.

Below we give the spectra of these products.

Spectrum of the products of isomerization of 1,3,5-trimethylcyclohexane, obtained at the boiling point of the hydrocarbon: 252(1), 325(1), 397(0.7), 406(3 broad), 434(2), 461(5), 499(2.2), 518(2.5), 556(0.5), 671(0.2), 704(1), 723(1.5), 746(3), 786(0.8 broad), 845(0.8), 947(0.5), 985(0.3), 1003(0.2), 1046(2), 1073(1), 1170(4 broad), 1211(0.3), 1267(1 broad), 1305(0.5), 1347(3.5 broad), 1443(1), 1460(10).

The spectra of the isomerization products of n- and isopropylcyclohexane in this series of experiments were similar to the spectrum of the products of isomerization of n- and isopropylcyclohexane at 100°.

SUMMARY

No ring isomerization and only isomerization resulting from the transference and disproportionation of radicals, occurred in the reaction of aluminum chloride with 1,3,5-trimethylcyclohexane, n- and isopropylcyclohexane at 100° as well as at the boiling points of the hydrocarbons.

The isomerization products were mixtures of 1,1,3-, 1,1,4-, 1,2,4- and 1,3,5-trimethylcyclohexane, in which approximately 50% was 1,1,3- and 1,1,4-trimethylcyclohexane.

LITERATURE CITED

[1] N. D. Zelinsky, M. B. Turova-Polyak, N. F. Tsvetkova and E. G. Treshchova, J. Gen. Chem. 21, 2156 (1951).

[2] R. Stratford, Am. offic. p. Nat. combustibles Liquides, 4, 83, 317 (1929); H. Pines, V. Ipatieff, J. Am. Chem. Soc. 61, 1076 (1939); S. D. Mekhtiev, Proc. Acad. Sci. USSR 1953, 140, 849; G. Chiurdoglu, Bull. Soc. Chim. Belg. 59, 156 (1950); 60, 39 (1951).

[3] M. B. Turova-Polyak and F. P. Sidelkovskaya, J. Gen. Chem. 11, 821 (1941).

[4] M. B. Torova-Polyak and A. F. Koshelev, J. Gen. Chem. 9, 2179 (1939).

[5] M. B. Turova-Polyak and E. N. Petrova, J. Gen. Chem. 16, 829 (1946).

[6] P. A. Bazhulin et al., Bull. Acad. Sci. USSR, Div. Chem. Sci. 1946, 12.

[7] G. Chiurdoglu, Bull. Soc. Chim. Belg. 59, 160, 168 (1950).

[8] F. Signaigo, P. Cramer, J. Am. Chem. Soc. 55, 3326 (1933).

[9] G. Chiurdoglu, Bull. Soc. Chim. Belg. 60, 43 (1951).

[10] A. Bag, T. Egupov and D. Volokitin, Ind. Org. Chem. 2, No. 15-16, 141 (1936); N. Shuikin, I. Dmitriev and G. Dobrynina, J. Gen. Chem. 10, 969 (1940).

[11] A. Forziati and F. Rossiai, J. Research. Nat. Bur. Standards 43, 473 (1949).

[12] M. D. Tilicheev, P. A. Akishin, E. G. Treshchova and V. M. Tatevsky, Factory lab. No. 9, 1080 (1948).

Received December 15, 1955

Moscow State University

THE REACTION OF ISOVALERALDEHYDE WITH A SOLUTION OF SODIUM ISOAMYLATE IN ISOAMYL ALCOHOL

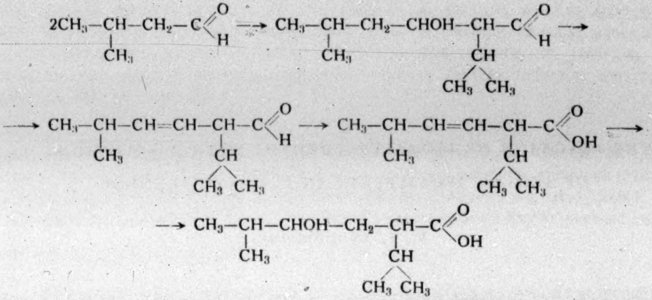
V. I. Lyubomilov

The analogy made earlier [1] between the reaction of aldehydes with alkali metal alcoholates and the reactions used to obtain divinyl from alcohol by Lebedev's method and by alcohol condensation using the Markovnikov-Gerbe method suggests that this reaction may be considered as the prototype of these important reactions. However, there has been comparatively little investigation of reactions of aldehydes and ketones with alkali metal alcoholates. There are papers by Verley [2] and Ponndorf [3] on this subject and others, similiar to it, where only the reducing effect of these alcoholates on the carbonyl group was investigated. Weizmann et al. [4] reduced not only the carbonyl group but also the double bond of an α,β-unsaturated aldehyde with an alkali metal alcoholate. The simultaneous condensing and reducing effect of alcoholates on aldehydes or ketones was observed in the papers by Haller and March [5], Lyubomilov and Terentyev [1] and Pratt and Kubler [6]. Mastagli's paper [7] on the effect of aldehydes on an alcohol solution of caustic potash may also be considered with this group. The formation of compounds corresponding to the reduction products of substances, formed by aldol condensation with subsequent aldehyde crotonization, was observed in these investigations. By this method, saturated and α,β-unsaturated alcohols with branching at the α-carbon atom were obtained.

In the present work isovaleraldehyde was treated with a solution of sodium isoamylate in isoamyl alcohol. We investigated the effect of temperature and time of reaction on the amount of saturated and unsaturated C_{10} alcohols and other reaction products formed. As can be seen from the data in Table 1, the amount of C_{10} alcohols increased with an increase in the reaction temperature and time. The relative amount of unsaturated C_{10} alcohol meantime decreased which can be seen by the decrease in the bromine numbers of these fractions. The high boiling condensation products were formed in a large amount under milder reaction conditions. Further, the reaction products were investigated in detail. We did not try to find out the effect of reaction conditions on the amount of each component formed but investigated the mixture of products obtained from experiments carried out under various conditions. The separation of neutral and then acidic products was carried out by fractional distillation. The fractions and fraction groups obtained were thoroughly investigated.

A small amount of aldehydes, probably of the saturated series, and three alcohols with extremely close boiling points were found in the neutral reaction products (after distilling off the excess isoamyl alcohol). Two of the alcohols were $C_{10}H_{20}O$ alcohols and one belonged to the saturated series $C_{10}H_{22}O$. The unsaturated alcohol with b.p. 201.5-202° gave 2,6-dimethyl-3-methylolheptane on hydrogenation and when oxidized with potassium permanganate, gave isobutyric acid and 5-methyl-2-isopropyl-4-hydroxy-3-ketocaproic lactone. This established its structure as 2,6-dimethyl-3-methylolheptene-4. This alcohol could have been formed by the reduction of the carbonyl group of the corresponding β,γ-unsaturated aldehyde. Such carbonyl compounds are known. Thus, for example, two isomers of mesityl oxide have been isolated [8] which differed in the α,β- and β,γ-position of their double bond. The second unsaturated alcohol was 2,6-dimethyl-3-methylolheptene-3, as can be seen by comparing its properties with those of authentic 2,6-dimethyl-3-methylolheptene-3. The saturated alcohol was 2,6-dimethyl-3-methylolheptane as it was identical with the one obtained by hydrogenation of 2,6-dimethyl-3-methylolheptene-3. Glycols were also among the neutral products with high boiling points as is shown by the high hydroxyl content of some fractions.

The acidic condensation products consisted mainly of isovaleric acid, while the products with high boiling points were mainly lactones. The lactone $C_{10}H_{18}O_2$ was isolated in a rather pure form and it was probably the γ-lactone of 5-methyl-2-isopropyl-4-hydroxycaproic acid, formed by the scheme:



The other lactone with higher boiling point could, presumably, have been the δ-lactone, of 7-methyl-2,4-diisopropyl-5-hydroxycaprylic acid, greatly contaminated with impurities. These lactones were together with a mixture of saturated and unsaturated acids of the C_{10} and C_{15} series.

EXPERIMENTAL

The Reaction of Sodium Isoamylate with Isovaleraldehyde

Into a flask with a stirrer, a reflux condenser, a thermometer and a dropping funnel, we loaded 176 g of isoamyl alcohol and dissolved 11.5 g of metallic sodium in it at 100-110°. Then, over a period of 30 minutes, 43 g of freshly distilled isovaleraldehyde (b.p. 91°) was added. At the end of the addition, the reaction mixture was either kept at this temperature or quickly cooled and washed with water to a neutral reaction. The alcohol layer was distilled in vacuum with a small fractionating column; fractions of isoamyl alcohol and condensation product were collected in the ranges from 96-98° (20 mm) to 105-106° (10 mm), which corresponded to C_{10} alcohols. The residue in the distillation flask consisted of high boiling condensation products. We determined the bromine number of the C_{10} alcohol fraction by the bromide-bromate method or by Kaufman's method. It is expressed in mg Br per g of sample. The washing water was concentrated and acidified with the calculated amount of sulfuric acid. The organic acid was isolated by the usual method. The data on the experiments carried out are given in Table 1.

TABLE 1

Condensation of Isovaleraldehyde with Sodium Isoamylate

Experiment No.	Temperature	Yield (in g)			Bromine number of C_{10} alcohol fraction
		C_{10} alcohol fraction	High boiling alcohols	Acid products	
1	110°	19.5	21.0	9.7	844.5
2	120	25.3	13.0	12.1	854.0
3	130	27.1	8.8	9.8	861.0
4	140	30.4	9.0	12.2	747.7
5	140	33.2	7.0	10.6	511.5

Footnote. In all the experiments the aldehyde was run in over 30 minutes; in experiments 1-4 there was no further heating, in experiment 5, heating was continued for 2 more hours.

The neutral condensation products, obtained as described above from experiments carried out under various conditions, were combined and carefully fractionated in vacuum on a column 1.7 m high and 22 mm diameter. The packing was "Raschig rings" cut from glass tubing 4 mm in diameter. The distillation rate was 4-5 drops per minute at a reflux ratio of 10-20. 157 g of material was fractionated. At the end of the fractionation, the high boiling condensation products were added to the residue in the distillation flask and distilled from a Claisen flask with a high side arm.

The aldehyde fractions (8.2 g) had b.p. from 50.5° (4 mm) to 64.5° (3.5 mm). The aldehyde content (with hydroxylamine, calculated on a molecular weight of 156) was 39.5%.

2,6-Dimethyl-3-methylolheptene-4. Yield 48.9 g. The constants and derivatives are given in Table 2.

Found %: C 77.1, 76.9; H 12.4, 12.8; OH 10.95, 11.38; bromine number 1018, 1034. $C_{10}H_{19}OH$ Calculated %: C 76.9; H 12.9; OH 10.89; bromine number 1024.

For the catalytic hydrogenation of 2,6-dimethyl-3-methylolheptene-4 we used 6 g of the material, about 2 g of Raney catalyst and 4 ml of ethyl alcohol. 856 ml (NTP) of hydrogen was absorbed when the amount calculated for $C_{10}H_{19}OH$ was 863 ml. The yield was 4.9 g.

B.p. 73.5-74.7° (3.5 mm), d_4^{20} 0.8352, n_D^{20} 1.4372.

The constants of the material obtained corresponded almost exactly with the constants of 2,6-dimethyl-3-methylolheptane, prepared by hydrogenating the corresponding unsaturated aldehyde (see below).

For the oxidation of 2,6-dimethyl-3-methylolheptene-4 we placed 6.5 g of the material and 50 ml of water in a flask with a stirrer and a dropping funnel. Over a period of 2 hours a solution of 25 g of potassium permanganate in 600 ml of water was run in. The neutral product was distilled off in steam. The manganese dioxide precipitate was filtered off and washed with hot water. The filtrate and water washings were concentrated to approximately 30 ml and acidified with 4.5 ml of sulfuric acid in 10 ml of water. The acids were extracted with ether and dried with baked sodium sulfate, the ether was distilled off and the acids were distilled in vacuum.

The yield was 1.5 g fraction with b.p. 80-82° (43 mm), d_4^{20} 0.9535, n_D^{20} 1.3945. Found: acid number 629. $C_4H_8O_2$. Calculated: Acid number 636.

The silver salt was prepared by the usual method.

Found %: Ag 54.7. $C_4H_7O_2Ag$. Calculated %: Ag 55.3.

The anilide was prepared by treating 1.3 g of the material with thionyl chloride and subsequently boiling the acid chloride with a solution of 2 g of aniline in 3 ml of benzene. The m.p. was 103.5-104°. The m.p. reported for isobutyric anilide is 105° [9].

The fraction with b.p. 131-145° (5 mm) (1.1 g) crystallized on standing. M.p. 178-179° (from dilute alcohol); the colorless crystals were flat needles, which were insoluble in water and petroleum ether but soluble in alcohol and benzene.

Found %: C 65.6, 65.2; H 8.30, 8.60. Esterification number 307. $C_{10}H_{16}O_3$. Calculated %: C 65.2; H 8.70. Esterification number 305.

2,6-Dimethyl-3-methylolheptene-3 was isolated from the fractions following fractions of 2,6-dimethyl-3-methylolheptene-4 and consisting of a mixture of 2,6-dimethyl-3-methylheptene-3 and 2,6-dimethyl-3-methylolheptane, by repeated careful fractionation of them in vacuum on a pear column 1 m high. The constants are given in Table 2.

Found %: C 77.30; H 12.60; OH 11.10. Bromine number 1021. $C_{10}H_{19}OH$ Calculated %: C 76.92; H 12.88; OH 10.89. Bromine number 1024.

2,6-Dimethyl-3-methylolheptane was isolated by fractional distillation after the previous removal of the unsaturated alcohols by oxidation with an aqueous solution of potassium permanganate. The constants are given in Table 2.

A fraction (5.5 g) containing glycol was obtained.

B.p. 110-113° (2 mm), d_4^{20} 0.9154, n_D^{20} 1.4608. Found %: OH 14.2. $C_{15}H_{32}O_2$. Calculated %: OH 13.8.

2,6-Dimethyl-3-methylalheptene-3 was prepared by the method of Batalin and Slavina [10] for the preparation of 2-ethylhexen-2-al from butyraldehyde. However, the condensation of isovaleraldehyde had to be carried out at a slightly higher temperature (75°) and for a slightly longer time (4 hours). Otherwise the corresponding aldol mainly formed and much of the isovaleraldehyde remained unreacted. From 200 g isovaleraldehyde we obtained 101.2 g (65.5%) of 2,6-dimethyl-3-methylalheptene-3 and recovered 27 g of unreacted isovaleraldehyde. By repeated fractionation on a pear column 1 m high, we obtained a narrow fraction of 2,6-dimethyl-3-methylalheptene-3 with the constants and derivatives given in Table 2.

Synthesis of 2,6-dimethyl-3-methylolheptane. 5.0 g of 2,6-dimethyl-3-methylalheptene-3 in 8 ml of alcohol was hydrogenated catalytically at room temperature over 2.5 g of Raney nickel. 1465 ml (NTP) of hydrogen was absorbed while the calculated amount was 1455 ml. After filtration, evaporating off the alcohol and distilling in vacuum, we isolated 3.5 g of material whose constants are given in Table 2.

Found %: OH 11.0. $C_{10}H_{21}OH$. Calculated %: OH 10.8.

TABLE 2

Properties of the Products Obtained

Sample No.		Boiling point at the given pressure (mm)	d_4^{20}	n_D^{20}	Derivative
1	2,6-Dimethyl-3-methylolheptene-4	201.5-202°(761), 67-67.5°(4)	0.8345	1.4440	α-Naphthylurethan, m.p. 64°
2	2,6-Dimethyl-3-methylolheptene-3	204-204.5°(742), 68.5-69.5°(4),*	0.8496	1.4521	α-Naphthylurethan, m.p. 69-69.5°
		66-67°(3.5)**	0.8485	1.4512	m.p. 67.8-68.5°
3	2,6-Dimethyl-3-methylolheptane	209-209.5°(761)*	0.8347	1.4372	α-Naphthylurethan, m.p. 47.5-48.2°
		208-209°(748)**	0.8361	1.4370	m.p. 48.5°
4	2,6-Dimethyl-3-methylalheptene-3	49.5-50°(3.5)	0.8454	1.4519	2,4-Dinitrophenylhydrazone m.p. m.p. 138.7°
5	5-Methyl-2-isopropyl-4-hydroxycaproic lactone	98-102°(4)	0.9906	1.4608	–

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* Data referring to the synthetic material.

** Data referring to the material isolated.

Synthesis of 2,6-dimethyl-3-methylolheptene-3. Into a flask fitted with a pear fractionating column 20 cm high, we placed 33.0 g of 2,6-dimethyl-3-methylalheptene-3, 43.7 g of aluminum isopropoxide and 102 g of isopropyl alcohol. The flask was heated on an oil bath so that the distillation went slowly until there was no acetone in the distillate. After the usual working up and fractionation, we obtained 18.8 g (57 %) of a material with the constants given in Table 2.

Found %: OH 10.75, Bromine number 1019. $C_{10}H_{19}OH$ Calculated %: OH 10.89. Bromine number 1024.

The acid products, obtained in different condensations of isovaleraldehyde with sodium isoamylate, were combined (70.8 g) and slowly fractionated in vacuum on a pear column 20 cm high. From the lower boiling fractions we isolated 33 g of isovaleric acid.

B.p. 55.5° (4.5 mm), d_4^{20} 0.9310, n_D^{20} 1.4038.

Acid number 548.5. $C_5H_{10}O_2$. Calculated: Acid number 549.4. Literature data: b.p. 59.6° (5 mm) [11], $d^{17.6}$ 0.9332, $n_D^{22.4}$ 1.4018 [12].

The higher boiling fractions contained a γ-lactone. Of the 11 g obtained, 5 g was washed with soda solution and water and distilled in vacuum from a Claisen flask. We obtained 2.6 g of a quite mobile, light yellow liquid, which, according to analysis, was 5-methyl-2-isopropyl-4-hydroxycaprylic lactone. The constants are given in Table 2.

Found %: C 70.20; H 9.00. Esterification number 332.8; bromine number 25. $C_{10}H_{18}O_2$. Calculated %: C 70.59; H 10.60. Esterification number 329.9.

On mixing with warm caustic soda solution, the product dissolved completely and on acidification it separated out unchanged. By hydrolyzing a sample of the lactone with excess caustic soda, neutralizing the excess alkali and adding silver nitrate, we obtained the silver salt of the corresponding acid, which was washed with water, dried in a desiccator and analyzed.

Found %: Ag 37.4. $C_{10}H_{19}O_3Ag$. Calculated %: Ag 36.6.

The soda solution from washing the γ-lactone was concentrated and acidified with sulfuric acid. About 1.5 g of an organic acid was isolated.

Found: Acid number 352, bromine number 340. $C_{10}H_{20}O_2$. Calculated: Acid number 326.

A lactone was isolated from the following fractions with lower acid numbers and after working it up as described above, we obtained 4.5 g of material.

B.p. 127-133° (4 mm), d_4^{20} 0.9480, n_D^{20} 1.4666.
Found: M 222; esterification number 196, acid number 2.0, bromine number 26. $C_{15}H_{28}O_2$. Calculated: M 240; esterification number 234.

In Table 2 we give the properties of the compounds isolated and prepared in this work.

SUMMARY

1. At 110-140° isovaleraldehyde reacts with a solution of sodium isoamylate in isoamyl alcohol to form mainly: 2,6-dimethyl-3-methylolheptene-3, 2,6-dimethyl-3-methylolheptene-4, 2,6-dimethyl-3-methylolheptane and, probably, a certain amount of glycols and higher alcohols as well as isovaleric acid, saturated and unsaturated acids of the C_{10} and C_{15} series and hydroxy acids, which were isolated in the form of the corresponding lactones.

2. In the products obtained at reaction temperatures of 110-130°, mainly unsaturated alcohols were found among the alcohols of the C_{10} series, with an increase in temperature or reaction time the amount of the C_{10} alcohol fraction increases as well as the relative amount of the saturated alcohol 2,6-dimethyl-3-methylolheptane.

LITERATURE CITED

[1] V. I. Lyubomilov and A. P. Terentyev, J. Gen. Chem. 21, 1479 (1951) (T.p. 1613).*

[2] M. Verley, Bull. Soc. Chim. (4) 37, 871 (1925).

[3] W. Ponndorf, Z. ang. Chem. 39, 138 (1926).

[4] Ch. Weizmann, M. Sulzbacher and E. Bergman, J. Chem. Soc. 1947, 851.

[5] A. Haller and F. March, Bull. Soc. Chim. 33, 969 (1905).

[6] E. F. Pratt and D. G. Kubler, J. Am. Chem. Soc. 76, 52 (1954).

[7] P. Mastagli, Ann. Chim. 10, 281 (1938).

[8] F. H. Stross, J. M. Monger and H. M. Finch, J. Am. Chem. Soc. 69, 1627 (1947).

[9] V. S. Johnson, R. D. Shennan and R. A. Rid, Organic Reagents for Organic Analysis (Moscow, 1948), 152.

[10] V. S. Batalin and S. M. Slavina, J. Gen. Chem. 7, 202 (1937).

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* T.p = C. B. Translation pagination.

[11] D. R. Stell, Tables of the Vapor Tensions of Individual Materials (Moscow, 1949), 16.

[12] Dictionary of Organic Compounds (Moscow, 1949), 470.

Received November 28, 1955

Institute of Scientific Investigation of Plastics

INVESTIGATIONS IN THE FIELD OF CONJUGATED SYSTEMS

LXVIII. DIENE SYNTHESES WITH FLUOROPRENE

I. CONDENSATIONS OF FLUOROPRENE WITH α,β-UNSATURATED ALDEHYDES AND KETONES

A. A. Petrov and A. V. Tumanova

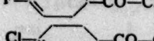
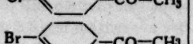
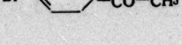
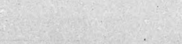
Organic fluorine compounds are lately becoming increasingly important in the syntheses of the most varied technically valuable materials: solvents, cooling agents, lubricants, plastics, new forms of benzene-frostproof rubber etc. [1]. 2-Fluorobutadiene-1,3-fluoroprene [2] is of great interest as it is a rubber former. Nevertheless, the chemical characteristics of this material, apart from its polymerization reaction, have hardly been studied.

Our aim was to complete, in some measure, the gaps existing in fluoroprene chemistry and we studied a series of reactions of this material, specifically, dimerization and diene synthesis with fluoroprene. There is data in the literature only on the condensation of fluoroprene with maleic anhydride, naphthoquinone [3] and tetrafluoroethylene [4]. Results of experiments on condensation of fluoroprene with acrolein, methyl vinyl ketone and methyl acetylenyl ketone are described in this report.

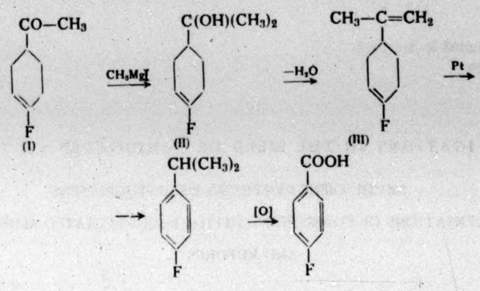
In analogy with the order of condensation of these materials with chloroprene [5], mainly para-substituted hydroaromatic compounds were expected in all cases. That the condensation product of fluoroprene with methyl acetylenyl ketone had such a structure was proved in this work.

Mainly polymers and a small amount of the trimer, the anticipated hydroaromatic aldehyde, were obtained by condensation of fluoroprene with acrolein. Trimer formation had been observed before in the condensation of chloroprene and bromoprene with acrolein [5].

Fluorotetrahydroacetophenone (I) was obtained in good yield by condensation of fluoroprene with methyl vinyl ketone. The constants of this material are compared in the table with those of unsubstituted tetrahydroacetophenone and its para-chloro- and bromo-substituted derivatives. It can be seen from the table data that (I) boils higher than the unsubstituted ketone and differs from all the other materials given in the table in its considerably lower refractive index which is characteristic of fluoro-substituted derivatives.

Materials	Boiling point at 20 mm	d_4^{20}	n_D^{20}	MR_D		Melting point	
				found	calculated	n-nitrophenylhydrazone	semicarbazone
 [6]	79.5—80°	0.9584	1.4698	36.09	36.49	142—143°	165—166°
	95—99.5	1.0705	1.4565	36.14	36.34	121—122	170—172
	120—120.5	1.1216	1.4972	41.38	41.35	165—166	179—180
	135—135.5	1.4176	1.5252	43.90	44.25	160—161	183—185

We tried to convert (I) into p-fluorobenzoic acid by the following scheme to establish its structure:



Ketone (I) was converted into the tertiary alcohol (II) by the action of methylmagnesium iodide. Alcohol (II) was a colorless, oily liquid with a flower-like smell. (II) had a higher boiling point and specific gravity and lower refractive index than the unsubstituted alcohol, obtained under the same conditions from tetrahydroacetophenone [7].

The hydrocarbon (III), presumably 4-fluoro-1-isopropenylcyclohexene-3, was obtained by dehydration of alcohol (II) with acetic anhydride. Hydrogen fluoride was separated in large quantities and unsubstitued cumene was the main product of dehydrogenating (III) over platinized charcoal. Thus, it was impossible to prove the position of the fluorine atom in the ring by the above schemes. Only the hydroaromatic character of (I) was proved.

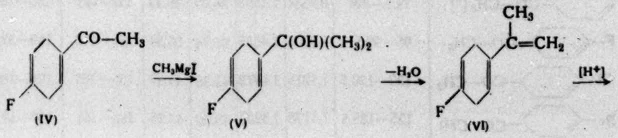
4-Fluoro-$\Delta^{1,4}$ -dihydroacetophenone (IV) which partially crystallized when cooled was obtained by condensation of fluoroprene with methyl acetylenyl ketone. The crystals, after washing with petroleum ether, melted at 42° and on standing, again gave an oil. The crystals and oil behaved the same chemically. Apparently, geometric isomers (IV) were formed by condensation of fluoroprene with methyl acetylenyl ketone and their existence was due to the nonplanar nature of the 1,4-cyclohexadiene ring.

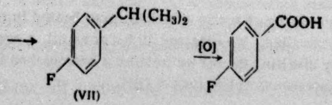
No condensation products were formed on heating (IV) with maleic anhydride. Therefore, the material did not have a conjugated system of double bonds. p-Fluoroacetophenone was obtained by dehydrogenating (IV) with chloranil. The oxidation of the former with dilute nitric acid gave p-fluorobenzoic acid. This reaction proved that the fluorine atom in (IV) was in the para-position to the acetyl group.

A tertiary alcohol (V), in the form of a colorless liquid with a pleasant smell, was obtained by treating (IV) with methylmagnesium iodide. The vinylcyclohexadiene fluorohydrocarbon (VI) was obtained by distilling (V) with a 10% solution of oxalic acid. The product was a colorless liquid with an aromatic smell. It readily decolorized bromine water.

(VI) was readily isomerized into p-fluorocumene by heating with hydrochloric acid on a water bath. Isomerization by acid is a normal property of vinylcyclohexadiene compounds [8]. As in a series of cases investigated earlier, the aromatic compounds boiled considerably lower than the isomeric vinylcyclohexadiene compound.

p-Fluorobenzoic acid with m. p. 181-183° was obtained by oxidizing p-fluorocumene with dilute nitric acid.





(VII)

The following conclusions may be drawn from a comparison of the results of experiments on the condensation of fluoroprene, chloroprene and bromoprene with unsaturated aldehydes and ketones: 1) the condensation product yield was considerably less in the reaction of acrolein with fluoroprene than in the reactions of this aldehyde with chloroprene and bromoprene, probably due to the greater activity of traces of hydrogen fluoride as catalysts for acrolein polymerization; 2) in reactions of fluoroprene with a ketone, the condensation product yield was correspondingly higher and, furthermore, a considerably lower degree of polymer formation was observed. This regular behavior was due to the weaker tendency of fluoroprene to polymerize, as compared with its analogs.

EXPERIMENTAL

1. Condensation of fluoroprene with acrolein. 21.6 g of fluoroprene, 20 g of acrolein, 20 ml of toluene and 0.5 g of hydroquinone were heated in sealed glass tubes at 120° for 12 hours. The reaction products were steam distilled. After the residues of acrolein and the toluene, a crystalline material began to come through in the condenser. After exhaustively distilling off this material, about 20 g of polymer remained in the flask.

From the condenser and the receiver we recovered 6.2 g (15%) of the trimer 4-fluoro-Δ^3-tetrahydrobenzaldehyde with m.p. 164-165° (after recrystallization from a mixture of alcohol and toluene).

Found %: F 14.49. M 383.6. $(C_7H_9OF)_3$. Calculated %: F 14.82. M 384.4.

The fluorine analysis of this and subsequent compounds was carried out by Elving and Ligett's method [9]. The molecular weight was determined cryoscopically in benzene.

2. Condensation of fluoroprene with methyl vinyl ketone. 38 g of fluoroprene, 38 g of methyl vinyl ketone and 0.5 g of hydroquinone in 48 ml of toluene were heated in sealed tubes at 140° for 10 hours. The reaction products were distilled in steam and then in vacuum. From this we obtained 55 g (73%) of 4-fluoro-Δ^3-tetrahydroacetophenone (I) with the constants given in the table.

Found %: F 13.46. $C_8H_{11}OF$. Calculated %: F 13.36.

The nitrogen derivatives of this ketone were prepared under the usual conditions. The melting points are given in the table. The p-nitrophenylhydrazone was recrystallized from aqueous ethyl alcohol.

Found %: N 15.26. $C_{14}H_{16}O_2N_3F$. Calculated %: N 15.16.

The 2,4-dinitrophenylhydrazone was recrystallized from ethyl alcohol.

Found %: N 16.93. $C_{14}H_{15}O_4N_4F$. Calculated %: N 17.39.

The semicarbazone was recrystallized from water.

Found %: N 21.42. $C_9H_{14}ON_3F$. Calculated %: N 21.10.

28.5 g of fluorotetrahydroacetophenone was added to an ice cold ether solution of the Grignard reagent, prepared from 5.6 g of magnesium and 40 g of methyl iodide. The mixture was worked up in the usual way to give 18.3 g (57.7%) of dimethyl-4-fluorocyclohexen-3-yl-carbinol (II).

B.p. 108-109° (20 mm), d_4^{20} 1.0478, n_D^{20} 1.4680, MR_D 42.00; calc. 42.52. Found %: F 12.50; OH 10.35. $C_9H_{14}(OH)F$. Calculated %: F 12.02; OH 10.74.

21 g of the alcohol (II) and 27 g of acetic anhydride were heated in sealed tubes at 200° for 8 hours. The reaction products were steam distilled. We obtained 12.5 g of an oil, a considerable part of which was unreacted alcohol (II) or its acetate. By distilling the oil we isolated a hydrocarbon fraction (4 g), which was apparently slightly impure 4-fluoro-1-isopropenylcyclohexene-3 (III).

B.p. 58-62° (20 mm), d_4^{20} 0.9255, n_D^{20} 1.4625. Found %: F 12.89. $C_9H_{13}F$. Calculated %: F 13.55.

By dehydrogenating (III) on platinized charcoal at 300°, we obtained cumol with slight impurity, which was apparently p-fluoroisopropylbenzene.

B.p. 151-153°, d_4^{20} 0.8854, n_D^{20} 1.4880.
Literature data for cumol [10]: b.p. 152.2°; d_4^{20} 0.8617, n_D^{20} 1.4913.
The constants of p-fluoroisoproylbenzene are given below.

3. Condensation of fluoroprene with methyl acetylenyl ketone. 20 g of fluoroprene, 60 ml of a toluene solution of methyl acetylenyl ketone (containing about 12% of the latter) and 0.2 g of p-tert.-butylpyrocatechol were heated at 120° for 12 hours. The yield of 4-fluoro-$\Delta^{1,4}$-dihydroacetophenone (IV) was 16.5 g (67%).

B.p. 105-106° (20 mm), d_4^{20} 1.1290, n_D^{20} 1.4922, MR_D 36.03; calc. 35.92. Found %: F 12.86. C_8H_9OF. Calculated %: F 13.55.

On cooling to − 10° the material partly crystallized. The crystals were filtered off and washed with petroleum ether. The yield was 2.6 g. The m.p was 41-42°. It was readily soluble in methyl and ethyl alcohols, ether and chloroform. Its deliquesced partly on storing.

Found %: F 13.08. C_8H_9OF. Calculated %: F 13.55.

1 g of ketone (IV) (the fraction 105-106° at 20 mm) was heated with 0.7 g of freshly distilled maleic anhydride in 10 ml of benzene on a boiling water bath for 3 hours. The mixture obtained was heated with 25 ml of 5% potassium hydroxide solution. The alkaline solution was acidified with sulfuric acid. Extraction of this solution with ether gave only maleic acid.

The nitrogen derivatives of the ketone (IV) were prepared by the usual method, by which they were made from the crystalline product and the original oil.

The 2,4-dinitrophenylhydrazone from both the products had the same m.p: 223-225° (from ethyl alcohol).

Found %: N 17.38. $C_{14}H_{13}O_4N_4F$. Calculated %: N 17.54.

The p-nitrophenylhydrazone from the crystalline material melted slightly higher than that from the original oil (221-222° and 213-215°).

Found for the first sample %: N 15.43, 15.36. $C_{14}H_{14}O_2N_3F$. Calculated %: N 15.26.

By treating 10.2 g of fluorodihydroacetophenone (IV) with the Grignard reagent prepared from 2.57 g of magnesium and 16 g of methyl iodide, we obtained 6 g (53%) of dimethyl-4-fluorocyclohexadien-1,4-yl-carbinol (V).

B.p. 100-102° (20 mm), d_4^{20} 1.1255, n_D^{20} 1.4910, MR_D 36.07; calc. 35.92. Found %: F 11.98. $C_9H_{13}OF$. Calculated %: F 12.16.

Distilling 6.5 g of (V) with a 10% solution of oxalic acid yielded 5.4 g of an oil, from which we isolated 4 g of a material, which was apparently 4-fluoro-1-isopropenyl-cyclohexadiene-1,4 (VI).

B.p. 75-77° (20 mm), d_4^{20} 1.0134, n_D^{20} 1.4990, MR_D 40.00; calc. 40.06. Found %: F 13.47. $C_9H_{11}F$. Calculated %: F 13.74.

2 g of (VI) was heated with 3 ml of acetic acid and 1 ml of concentrated hydrochloric acid in sealed tubes on a boiling water bath for 3 hours. The reaction products were steam distilled. The solution was washed with potash, dried over $CaCl_2$ and the p-fluorocumol (VII) was distilled in vacuum.

B.p. 54.5-55.5° (20 mm), d_4^{20} 0.9783, n_D^{20} 1.4716, MR_D 39.50; calc. 40.16. Found %: F 12.97. $C_9H_{11}F$. Calculated %: F 13.74.

0.25 g of fluorocumol was oxidized with 5 ml of 25% nitric acid on a boiling water bath for 8 hours. On cooling, crystals of p-fluorobenzoic acid separated. The m.p. was 181-183° (from hot water). A mixed m.p. with authentic p-fluorobenzoic acid was not depressed.

2.2. g of (IV) was heated with 3.7 g of chloranil in xylene solution for 4 hours. After the usual treatment, the mixture yielded 1.2 g of p-fluoroacetophenone.

B.p. 78.5-79° (12 mm), n_D^{20} 1.5100.
Literature data [11]: b.p. 79° (12 mm), n_D^{25} 1.5081.

By oxidizing the material with dilute nitric acid, we obtained p-fluorobenzoic acid with m.p. 179-181°.

SUMMARY

1. The condensation of fluoroprene with acrolein, methyl vinyl ketone and methyl acetylenyl ketone was investigated.

2. The trimer, the anticipated fluorotetrahydrobenzaldehyde, was obtained from fluoroprene and acrolein.

3. Fluorotetrahydroacetophenone was obtained from fluoroprene and acrolein, fluorodihydroacetophenone – from fluoroprene and methyl acetylenyl ketone. The structure of the latter product was proved by conversion into p-fluorobenzoic acid by two methods.

4. Tertiary alcohols were obtained by the action of a Grignard reagent on fluorotetrahydro- and fluorodihydro-acetophenones and from the alcohols we obtained fluoro hydrocarbons which were, presumably, 4-fluoro-1-isopropenylcyclohexene-3 and 4-fluoro-1-isopropenylcyclohexadiene-1,4. p-Fluorocumene was obtained by isomerization of the latter with hydrochloric acid.

5. The possibility of obtaining a series of fluoro-containing hydroaromatic compounds from fluoroprene by the method of diene synthesis was established.

LITERATURE CITED

[1] I. L. Knunyants and L. V. Fokin, Nature, No. 8, 3 (1955).

[2] I. L. Knunyants and L. V. Fokin, Progr. Chem. 20, 410 (1951).

[3] Amer. patent 2451612; Ch. A., 43, 2218 (1949).

[4] D. Coffman, P. Barrick, R. Cramer and M. Raasch, J. Am. Chem. Soc. 71, 490 (1949).

[5] A. A. Petrov and N. P. Sopov, J. Gen. Chem. 17, 1295 (1947).

[6] A. A. Petrov, J. Gen. Chem. 11, 309 (1941).

[7] A. A. Petrov and N. P. Sopov, J. Gen. Chem. 22, 591 (1952) (T.p. 653).*

[8] A. A. Petrov and N. P. Sopov, Proc. Acad. Sci. USSR 79, 811 (1951).

[9] Ph. Elving and W. Ligett, Ind. Eng. Chem. Anal. Edit. 14, 449 (1942).

[10] A. W. Francis, Chem. Revs. 42, 126 (1948).

[11] M. W. Renoll, J. Am. Chem. Soc. 68, 1159 (1946).

Received November 21, 1955

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* T. p. = C. B. Translation pagination.

HYDROLYSIS OF ALKYLDIOXANES

M. I. Farberov and N. K. Shemyakina*

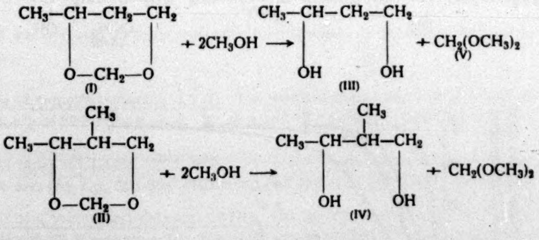
Alkyldioxanes-1,3 are presently technically available products as they are obtained in high yields by reaction of olefins with aldehydes in the presence of acidic catalysts [1]. Alkyldioxanes-1,3 are acetals (formals) of the corresponding diols-1,3, and like all acetals, are readily hydrolized by acid.

We were interested in the hydrolysis of alkyldioxanes as we considered that there was a possibility of using this reaction for diol-1,3 synthesis and of using the aldehydes, split off by the hydrolysis, for the quantitative determination of dioxanes.

Acetal hydrolysis is a reversible reaction and the equilibrium state, with all other conditions equal, depends on the nature of the alcohol (diol) and aldehyde [2]. It is necessary to remove the aldehyde from the sphere of the reaction as a compound, to obtain the fullest possible reaction.

For the diol synthesis, we carried out the alkyldioxane hydrolysis (methanolysis) in the presence of a small amount of sulfuric acid and excess methyl alcohol at the boiling point of the reaction mixture. The methyl alcohol combined with the aldehyde, separated as a low-boiling acetal (methylal), which was easily removed from the sphere of the reaction. (An analogous patent has been filed in the USA [3].)

The hydrolysis of 4-methyldioxane-1,3 (I) and 4,5-dimethyldioxane-1,3 (II) proceeded very smoothly. Under these conditions the only reaction products formed were the corresponding diols: butandiol-1,3 (III) and 2-methyl-butandiol-1,3 (IV). No side or tar-like products were formed. We succeeded in obtaining 80% and higher yields of diol. Formaldehyde was removed in the form of methylal (V).



The reaction proceeded much less smoothly for dialkyldioxanes which have the oxygen atom connected to a tertiary carbon atom.

In hydrolizing 4,4-dimethyl-dioxane-1,3 (VI), together with the diol, 3-methyl-butandiol-1,3 (VII), a considerable amount of the monomethyl ether of this diol, [3-methyl-3-methoxybutanol-1 (VIII)] was formed, as well as isoprene (IX) and an unsaturated alcohol (X). These products, apparently, were the results of further con-

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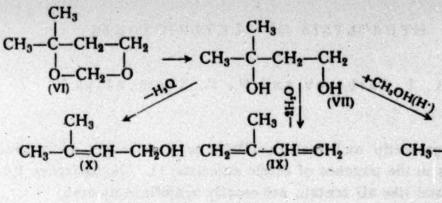
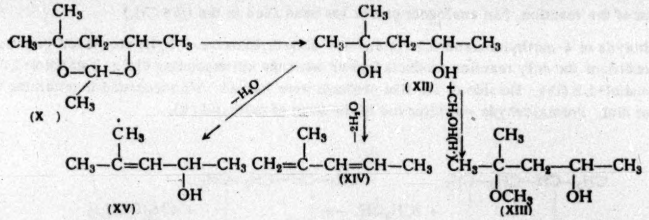
[*] E. N. Volkova took part in the experimental section.

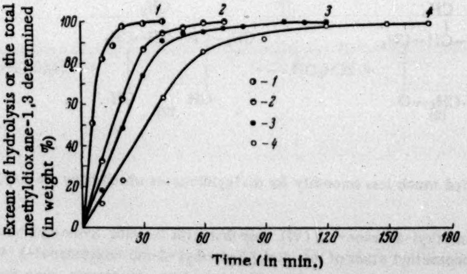
The hydrolysis of 2,4,4,6-tetra-methyldioxane-1,3 (XI) proceeded similiarly. The yield of 2-methylpentandiol-2,4 (XII) was in this case even less (18-25%); at the same time a considerable amount of monomethyl ether of this diol – 4-methyl-4-methoxypentanol-2 (XIII) – was formed, as well as methylpentadiene (XIV) and an unsaturated alcohol (XV). The aldehyde split out was removed as acetal:



As we had shown above, some diols (for example, butandiol-1,3) may be obtained by this method with yields close to quantitative, but at the same time a considerable amount of methylal was formed as a side product.

We carried out a series of experiments on the vapor-phase hydrolysis of methylal over solid catalysts with acidic properties. Methylal, diluted with water vapor (1 : 3 by weight) was passed over one of these catalysts at a volume rate of 0.35-0.4 (in ml per ml of catalyst per hour) at temperatures of 350-375°. The yield of formaldehyde and methyl alcohol was higher than 80% under these conditions. Without doubt this yield may be improved further.





The relation of the hydrolysis rate of 4-methyldioxane-1,3 at 100° to the acid concentration. Acidity (in weight %): 1) 3.0, 2) 0.5, 3) 0.25, 4) 0.05.

To determine alkyldioxanes analytically, we hydrolysed them in the presence of hydroxylamine salts, which combined with the aldehyde to form the oxime; at the same time an acid was separated quantitatively and was titrated with alkali [4].

An accurately measured amount of 10% sulfuric acid previously added to the analysis mixture to obtain an acidity of 0.25-0.5 weight %, helped to accelerate the hydrolysis process. The relation of hydrolysis rate of 4-methyldioxane (I) to acidity is shown in the figure. Thus, 4-methyldioxane-1,3 (I) hydrolysis was fully complete in 1-1.5 hours at an acid concentration of 0.25-0.5 weight %. The accuracy of the method was ± 1% (abs.).

The analysis results obtained by this method for dimethyldioxanes and tetramethyldioxanes had to be divided by 0.9. This correction took into account side reactions, which have not yet been clarified.

EXPERIMENTAL

As starting materials we used technical alkyldioxanes, which had been distilled on a laboratory column of 50 theoretical plates.

The constants and other data for the alkyldioxanes used are given in the table.

The hydrolysis of the alkyldioxanes was carried out in a flask, connected to a laboratory fractionating column, by gently boiling the reaction mixture. Methylal (acetal) was taken off at 41-44° (57-60° for acetal). At the end of the reaction, the flask was cooled and the mixture was neutralized with sodium carbonate. The reaction products were then distilled in vacuum; pure products were isolated by a second distillation.

Sample No.	Alkyldioxane	Boiling point	n_D^{20}	d_4^{20}	Method of preparation	Yield (in %)
1	4-Methyl-dioxane-1,3 (I)	115.3°	1.4159	0.9758	From propylene and formaldehyde	80-85
2	4,4-Dimethyl-dioxane-1,3 (VI)	133.4	1.4238	0.9634	From isobutylene and formaldehyde	75-80
3	4,5-Dimethyl-dioxane-1,3 (II)	133.5	1.4223	0.9630	From butene-2* and formaldehyde	90-92
4	2,4,4,6-Tetramethyldioxane-1,3 (XI)	140.2	1.4192	0.9039	From isobutylene and acetaldehyde	90-92

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[*] The butene-2 was obtained by sharp separation from butene-1 in the butene fraction on a 100 plate semi-industrial column.

Hydrolysis of 4-methyl-dioxane-1,3 (I). The reaction charge was 1 mole (102 g) of the material, 3 moles of CH_3OH and 2.5% of 92% sulfuric acid. We obtained 73.9 g (82%) of butandiol-1,3 (III).

B.p. 92° (3 mm), n_D^{20} 1.4400, d_4^{20} 1.0027.
Literature data [5]: b.p. 203-204° (760 mm), 114° (20 mm), n_D^{20} 1.4418, d_4^{20} 1.0053.

Hydrolysis of 4,5-dimethyl-dioxane-1,3 (II). The reaction charge was 1 mole (116 g) of the dioxane, 5 moles of CH_3OH and 5% of sulfuric acid. The yield was 83 g (80%) of 2-methyl-butandiol-1,3 (IV).

B.p. 92° (6 mm), n_D^{20} 1.4478, d_4^{20} 0.9919, MR_D 28.04; calc. 27.94. Found %: C 57.71, 57.58; H 11.97, 11.85; OH 31.1 (phthalylation). $C_5H_{12}O_2$. Calculated %: C 57.70; H 11.52; OH 32.66.

Hydrolysis of 4,4-dimethyl-dioxane-1,3 (VI). The charge was 1 mole (116 g) of dioxane, 5 moles of CH_3OH and 1% of sulfuric acid. During the reaction there was noticeable separation of isoprene (b.p. 32-33° gave adduct with maleic anhydride) together with methylal. In the fraction distilling up to 50° (50 mm), we found an unsaturated alcohol, which was determined by the bromide-bromate method and also by phthalylation.

On conversion to unsaturated alcohol, the results of both methods coincided. This alcohol was not examined more closely.

The higher boiling products were further distilled; this yielded two products: 1st with b.p. 63° (7 mm) 28.75 g; 2nd with b.p. 95° (7 mm) 35.5 g.

3-Methyl-3-methoxy-butanol-1 (VIII) (1st product). The yield was 27.7%.

n_D^{20} 1.4272, d_4^{20} 0.9220, MR_D 33.0; calc. 33.076. Found %: C 60.89, 60.70; H 12.4, 11.97; OH 13.7 (phthalylation); OCH_3 29.02. $C_6H_{14}O_2$. Calculated %: C 61.01; H 11.94; OH 14.4; OCH_3 29.2.

3-Methyl-butandiol-1,3 (VII) (2nd product). The yield was 38.7%.

n_D^{20} 1.4420, d_4^{20} 0.9763.
Literature data [6]: b.p. 109-110° (17 mm), n_D^{20} 1.4452, d^{15} 0.985.

Hydrolysis of 2,4,4,6-tetramethyldioxane-1,3 (XI). 40.25 g of dioxane, 44.7 g of CH_3OH and 0.9 g of sulfuric acid were used. After distilling off the acetal, a small amount of material was obtained with b.p. 73-75°, which was characterized as 2-methylpentadiene (XIV). The adduct of (XIV) with maleic anhydride had m.p. 57.8-59.1°. Literature data for the adduct: m.p. 57° [7].

The fraction, distilling up to 70° (at 30 mm) contained 5.5 g of unsaturated alcohol, which was determined by the bromide-bromate method and by phthalylation (the two methods gave similar results, calculated for the alcohol $C_6H_{12}O$).

The high boiling products were further distilled; this yielded two products: 1st with b.p. 163-164°, 8.8 g; 2nd with b.p. 101° (9 mm), 5.6 g.

4-Methyl-4-methoxy-pentanol-2 (XIII) (1st product) was isolated in a slightly impure state in 25.5% yield.

n_D^{20} 1.4237, d_4^{20} 0.8993, MR_D 37.69; calc. 37.40. : Found %: OCH_3 23.5; OH 12.4 (phthalylation), $C_7H_{17}O_2$. Calculated %: CH_3O 21.1; OH 12.8.

4-Methyl-pentandiol-2,4 (XII) (2nd product). The yield was 18.2%.

n_D^{20} 1.4280, d_4^{20} 0.9311, MR_D 32.6; calc. 33.09. Found %: C 61.40; H 11.42. Calculated %: C 61.52; H 11.85.

Vapor phase hydrolysis of methylal. The experiments were carried out in a silica catalyst tube inside a tubular furnace. In one typical, steady experiment we passed methylal and water through 35 ml of catalyst at volume rates of 0.382 and 1.15 respectively (in ml per ml of catalyst per hour). During the experiment the temperature was kept at 375° (±2°). The experiment was continued for 1 hour. The total methylal passed through in the experiment was 24 g (0.316 moles). The "furnace" condensate (111 g) was analyzed for formaldehyde (iodometric method), methanol (phthalylation method) and recovered methylal (hydrolysis in the presence of hydroxylamine hydrochloride). The content of these substances in the condensate (in weight %) was: formaldehyde 7.0, methanol 14.6 and recovered methylal 0.65. Thus we found: formaldehyde 7.75 g (0.258 moles) (yield 81.8% on methylal passed through and 84.2% on decomposition) and methanol 16.2 g (0.506 moles) (respective yields: 80 and 82.5%).

The analytical determination of the alkyldioxanes was carried out in the following way. Samples of 0.5-0.7 g (calculated on the pure dioxane) were placed into ampoules, closed with rubber bungs. Then 25 ml of 1 N hydroxylamine salt solution was introduced together with an exactly measured amount of 10% sulfuric calculated to give an acidity of 0.5%. The ampoules were closed and placed in a boiling water bath. The contents of the ampoules were quantitatively transferred to 250 ml conical flasks and titrated with 0.25-0.5 N caustic soda solution in the presence of bromophenol blue. Parallel with this we determined the acidity of 25 ml of 1 N hydroxylamine salt solution, acidified with the same amount of acid.

The calculation was carried out by the formula $Q = \frac{(a-b)\,k \cdot c \cdot 100}{d}$, where: Q – the dioxane content of the sample examined (in weight %); a – the amount of alkali in milliliters, used to titrate the sample; b – the normality; c) amount of dioxane (in grams) equivalent to 1 ml of alkali solution; d) weight of the sample (in grams).

SUMMARY

1. The hydrolysis of a series of alkyldioxanes-1,3 has been studied in the presence of acids (as catalysts) and methyl alcohol (for shifting the equilibrium).

2. It was shown that the following diols could be obtained in very high yields by this method: butandiol-1,3 was obtained from 4-methyldioxane-1,3 and 2-methyl-butandiol-1,3 from 4,5-dimethyldioxane-1,3. No side products were found in the hydrolysis of these dioxanes.

3. The reaction was more complicated for alkyldioxanes whose oxygen atom is connected to a tertiary carbon atom (4,4-dimethyldioxane-1,3 and 2,4,4,6-tetramethyldioxane-1,3) as beside the corresponding diols, diol monethers, unsaturated alcohols and dienes were formed.

4. It was shown that methylal, which formed during alkyldioxane hydrolysis (methanolysis), itself readily underwent vapor-phase hydrolysis over a catalyst with the formation of formaldehyde and methanol.

5. A method was proposed for the quantitative determination of alkyldioxanes-1,3 based on their hydrolysis in the presence of hydroxylamine salts.

LITERATURE CITED

[1] E. Arundale and L. Mikeska, Chem. Revs. 51, 505 (1952); Prog. Chem. 23, 223 (1954).

[2] Adkins and Adams, J. Am. Chem. Soc. 47, 1368 (1925).

[3] Amer. Patent 2421862; C. A. 41, 5894 (1947).

[4] S. Siggia, Quantitative organic analysis via functional groups (1949), N. Y., 163.

[5] Bergmann, Mickeley and Lippmann, Ber. 62, 1474 (1929).

[6] M. Davydova, Z. Papkina and D. Tishchenko, J. Gen. Chem. 7, 1942 (1937).

[7] G. Bachman and G. Goebel, J. Am. Chem. Soc. 64, 787 (1942).

Received November 2, 1955

Yaroslav Institute of Technology and
Experimental Plant of the Ministry of
Chemical Industry of the USSR

THE ALKYLATION OF BENZENE WITH DI-(1-HYDROXY)-CYCLOHEXYLACETYLENE MONOACETATE IN THE PRESENCE OF $AlCl_3$

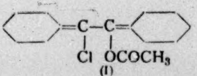
R. M. Lagidze, N. K. Iremadze and L. P. Chigogidze

It was shown in previous papers [1-3] that the crystalline hydrocarbons $C_{14}H_{10}$, $C_{14}H_{16}$ and $C_{18}H_{20}$ are formed by benzene alkylation with diacetates of butyndiol-1,4, tetramethylbutyndiol and 1,1'-ethynylbicyclopentanol. Beside these compounds, 1-chloro-4-acetoxybutyne-2, 2,5-dimethyl-3-chloro-4-acetoxyhexadiene-2,4, 1-chloro-2-acetoxy-1,2-dicyclopentylideneethane and 1-acetoxy-2-phenyl-1,2-dicyclopentylideneethane were isolated from the intermediate condensation products as well as from the products of the direct reaction of anhydrous $AlCl_3$ with the diacetates of the given glycols. The isolation of the last of the three products made it possible to carry out its intramolecular cyclization in a neutral medium and to obtain the same hydrocarbon $C_{18}H_{20}$.

Di-(1-hydroxy)-cyclohexylacetylene monoacetate was used in the present work to obtain analogous compounds. Although alkylation of benzene by either the monoacetate or the diacetate gives the same hydrocarbon with m.p. 188-189°, in this case the monoacetate was preferred as the reaction with it was smoother and gave a better yield. However, as the same hydrocarbon with m.p. 188-189° was obtained in both cases, to study its formation mechanism, the reaction of anhydrous $AlCl_3$ with di-(1-hydroxy)-cyclohexylacetylene diacetate was also investigated, in passing. 1-Acetoxy-2-chloro-1,2-dicyclohexylideneethane (I) or, what is less probable, its isomer with the double bonds in the rings (I') was obtained from this reaction. The chloroether (I) structure was confirmed by analytical data and by the identification of oxalic and adipic acids in its oxidation products.

3 fractions were separated from the condensation products of di-(1-hydroxy)-cyclohexylacetylene monoacetate with benzene: the 1st fraction was not investigated thoroughly; the 2nd fraction corresponded to a compound with the composition $C_{14}H_{20}O$. It absorbed approximately 2 moles of hydrogen when hydrogenated. When oxidized it gave oxalic and adipic acids. On the basis of these data, it may be conjectured that the material $C_{14}H_{20}O$ (II) was formed by acetylene-diene regrouping and subsequent splitting out of HCl from the product of the substitution of the monoacetate acyl group by chlorine. The third fraction was quite similiar in elementary composition to the hydrocarbon $C_{20}H_{24}$. Except for a slight deviation from the theoretical which apparently was due to the difficulties of purifying it by fractionation, the material obtained was identical with the crystalline hydrocarbon with m.p. 188-189°, which could be isolated from it. The hydrocarbon dissolved readily in benzene and chloroform, with considerably more difficulty in ether and very slightly in ethanol and methanol; it slowly decolorized dilute potassium permanganate solution and did not react with bromine water. Like all the hydrocarbons mentioned above, it did not hydrogenate over a platinum catalyst under the usual conditions. It did not give a picrate under any conditions and did not undergo diene condensation with maleic anhydride. As with the crystalline material with m.p. 188-189°, adipic, benzoic and o-phthalic acid were isolated and identified (the last only by a fluorescein reaction) from the oxidation products of the liquid hydrocarbon. The oxidation results show that a benzene ring is contained in the hydrocarbon molecule $C_{20}H_{24}$ connected in a definite manner (apparently, in the ortho-position) to the cyclohexylidene or cyclohexenyl radicals.

A crystalline material, corresponding to 2-phenylanthracene [4] in melting point, was obtained by dehydrogenation of the 3rd fraction over palladium-charcoal. On the basis of these data, it appears that, as in the case of hydrocarbons obtained earlier, the basic structural element of the hydrocarbon $C_{20}H_{24}$ (III or III') is the group (0,2,4)-bicyclooctatriene-2,4,6.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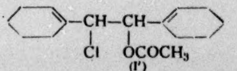
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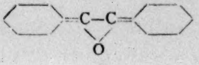
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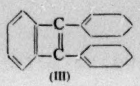
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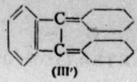
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EXPERIMENTAL

The di-(1-hydroxy)-cyclohexylacetylene synthesized by us had m.p. 101-102° and its diacetate had m.p. 45°, which completely agrees with the literature data [5]. The monoacetate, together with a small amount of the diacetate, was prepared under similar conditions by treating the glycol with the calculated quantity of acetic anhydride.

B.p. 136-138° (2-3 mm), d_4^{20} 1.0182, n_D^{20} 1.5092.
0.3255 g of material: 2.11 ml of 0.5 N alcoholic KOH solution. $C_{16}H_{24}O_4$. Calculated 2.4 ml of KOH.
A qualitative test for the acetylenic triple bond gave a positive reaction.

Reaction of anhydrous $AlCl_3$ with the diacetate. 6 g of $AlCl_3$ was added in separate portions with stirring to a solution of 20 g of the diacetate in 60 ml of dearomatized ligroin. The flask was heated on a water bath at 70° for 3-4 hours. The complex formed was decomposed with dilute acid, washed with dilute soda solution, then with water, extracted with ether, dried over Na_2SO_4 and the ether distilled off. The yield was 30%. Distillation of the residue yielded a fraction, corresponding to 1-acetoxy-2-chloro-1,2-dicyclohexylideneethane.

B.p. 138-142° (2-3 mm), d_4^{20} 1.0246, n_D^{20} 1.4925. Found %: Cl 12.40, 12.03. M 284, 276. $C_{16}H_{23}O_2Cl$.
Calculated %: Cl 12.30. M 282.5.

The fraction with b.p. 138-142° (2-3 mm) (1 g) was oxidized in the cold with 100 ml of 1% $KMnO_4$ in acetone, in the presence of 1.5 g of sodium carbonate. The precipitate was filtered off from the solution and washed with hot distilled water, the filtrate was acidified with dilute H_2SO_4 and extracted several times with ether. The flask containing the residue from evaporating off the ether was placed on a boiling water bath. After 2-3 hours sublimed crystals were found on the walls of the flask, which did not depress the melting point of authentic oxalic acid. In another experiment 1 g of material was oxidized under similar conditions with 100 ml of 2% aqueous $KMnO_4$. The filtrate was worked up in the usual way. The residue after the removal of the ether and oxalic acid (by sublimation) was recrystallized from dilute nitric acid. A substance was isolated with m.p. 148-150°, which did not depress the melting point of adipic acid.

Condensation of the monoacetate with benzene. The reaction was carried out in a three-necked, round bottomed flask, fitted with a mechanical stirrer and a reflux condenser. 25 g of the monoacetate was run dropwise into an ice water cooled, continuously stirred mixture of 80 g of benzene and 23.5 g of $AlCl_3$. After this the mixture was gradually heated on a water bath to 75-80° for 6 hours. The complex was worked up in the usual way to give 22.1 g of condensate, which yielded three fractions after several distillations: 1st fraction in about 9% yield (relative to condensate), b.p. 78-80° (2-3 mm), d_4^{20} 0.9643, n_D^{20} 1.5320. It gave a semicarbazone with m.p. 194. This fraction consisted mainly of acetophenone.

The 2nd fraction readily decolorized bromine water and dilute $KMnO_4$ solution. It did not give a qualitative reaction for an acetylenic bond. The yield was 5%.

B.p. 125-128° (2-3 mm), d_4^{20} 1.0292, n_D^{20} 1.5465. Found %: C 82.28; H 10.12. M 201.5, 210. $C_{14}H_{20}O$.
Calculated %: C 82.35; H 9.80. M 204.
0.6082 g of the material, dissolved in 25 ml of ethyl alcohol, combined with 115.73 ml of H_2 (NTP) in the presence of 0.2 g of platinum black. Calculated: 139.9 ml H_2.

From the oxidation of the 2nd fraction with potassium permanganate and also chromium trioxide in glacial acetic acid, we isolated and identified adipic and oxalic acids.

The 3rd fraction with b.p. 160-165° (1.5-2 mm), d_4^{20} 1.0328, n_D^{20} 1.5676 was a pale straw colored, thick, oily liquid. According to the elementary composition and the molecular weight, the freshly redistilled fraction was close to the hydrocarbon $C_{20}H_{24}$. On long standing it gradually changed into a crystalline compound. However this process took more than one year. In some cases the crystal formation was accelerated considerably by the addition of a small amount of ether and stirring with a glass rod. It was found that each time after the separation of the solid material, the residue again began to crystallize. During repeated distillation, a thin crystalline layer was often observed to form in parts of the side arm and the neck of the flask, especially after washing with ether. From two years observation of this fraction, we were convinced that it was almost completely converted into a solid hydrocarbon. The greatest deviation of the elementary composition from the theoretical, as was noted above, is explained by the difficulties of its purification. The solid mass, separated from it, after pressing in filter paper and recrystallization three times from an alcohol-benzene mixture, melted at 188-189°.

Found %: C 90.98, 91.11; H 8.86, 8.83. M 270.3. $C_{20}H_{24}$. Calculated %: C 90.91; H 9.09. M 264.

To oxidize the material with m.p. 188-189°, 1.5 g of sodium carbonate and 100-150 ml of 2% $KMnO_4$ solution was added to 1 g of it. It was heated on a boiling water bath with stirring. Powdered potassium permanganate was gradually added to the mixture in small portions until it was no longer decolorized. The precipitate was filtered off from the solution and washed with hot distilled water. The filtrate was decolorized with potassium bisulfate, acidified and extracted several times with ether. The ether extract was dried over Na_2SO_4, filtered and the solvent was slowly evaporated. After this the flask with the residue was placed on a boiling water bath and was heated for 2 hours. Onto its walls sublimed white, needle-like crystals with m.p. 119-120°, which did not depress the melting point of authentic benzoic acid. The residue, which also contained inorganic impurities, was treated several times with ether. The ether extract was evaporated first slowly and then on a boiling water bath until traces of solvent had been completely removed. The remaining yellowish, semisolid mass was recrystallized from dilute nitric acid, gently washed with water and dried. The material obtained in this way melted in the range 147-149° and did not depress the melting point of synthetic adipic acid.

In another experiment under similar conditions, 1.5 g of a liquid hydrocarbon was oxidized to give the same results. The o-phthalic acid in the mixture of oxidation products was identified in both cases by clearly expressed color effects of the fluorescein reaction.

1.5 g of material with b.p. 160-165° (1.5-2 mm) (3rd fraction) was dehydrogenated in a high-necked flask in the presence of 0.2 g of palladium black at 300-310° for a period of more than 30 hours in a continuous stream of dry CO_2. By working up the dehydrogenate under the usual conditions, we isolated a crystalline material with m.p. 207-208° (from benzene and ethyl acetate). A mixed melting point with synthetic 2-phenylanthracene (m.p. 203-204°), prepared by a known method [4] (melting 3-4° lower than reported in the literature after several recrystallizations), was not at all depressed.

SUMMARY

1. The possibility of forming polynuclear hydrocarbons was shown in the fourth example of the condensation of acetic esters of γ-acetylenic glycols with benzene in the presence of anhydrous $AlCl_3$.

2. A hydrocarbon with the composition $C_{20}H_{24}$ and a chloroester, corresponding to 1-chloro-2-acetoxyl-1,2-dicyclohexylidieneethane, or what is less probable, its isomer with double bonds in the rings, were isolated and characterized from the products of benzene alkylation with di(-hydroxy-)-cyclohexyl-acetylene monoacetate and from the reaction of anhydrous $AlCl_3$ with the diacetate of the same glycol.

LITERATURE CITED

[1] R. M. Lagidze, A. D. Petrov, Proc. Acad. Sci. USSR 83, 235 (1952).

[2] R. M. Lagidze, A. I. Dvalishvili, Repts. Acad. Sci. Georgian SSR 3, 205 (1955).

[3] R. M. Lagidze, N. R. Loladze, Repts. Acad. Sci. Georgian SSR 8, 607 (1955).

[4] J. Cook, J. Chem. Soc. 1930, 1091.

[5] I. M. Gverdtsiteli and Sh. G. Mikadze, Proc. Acad. Sci. USSR 89, 861 (1953).

Received May 21, 1955

Institute of Chemistry of the Academy
of Sciences of the Georgian SSR

A CONTRIBUTION TO THE SYNTHESIS OF TERTIARY ALCOHOLS BASED ON CAMPHOR. II

V. I. Esafov and N. I. Novikov

During investigations on the reaction of camphor with CH_3MgI we established [1] the formation of compounds, similiar in composition to the complexes discovered by V. M. Tolstopyatov [2]: $ROMgHal \cdot 2C_{10}H_{16}O$, where R may be $C_{10}H_{15}$, $C_{10}H_{17}$, $C_{11}H_{19}$, which corresponded to the complexes of camphor enolate, borneolate and methylborneolate. The formation of such compounds is the basic cause for the lower yields of tertiary alcohol methylborneol, when the reaction is carried out at − 15°.

It seemed interesting to find out how the reactions of $ROMgHal \cdot 2C_{10}H_{16}O$ as well as $MgHal_2 \cdot 2C_{10}H_{16}O$ would proceed at higher temperatures. It was possible that the phenomenon of complex formation could change from a factor with a negative effect on the normal Grignard reaction in the cold to a factor with a positive effect at higher temperatures.

Complexes with the following compositions were obtained for out purpose: $MgBr_2 \cdot 2C_{10}H_{16}O$ (I), $MgI_2 \cdot 2C_{10}H_{16}O$ (II) and $C_2H_5OMgI \cdot 2C_{10}H_{16}O$ (III) and their reactions with C_2H_5MgBr and CH_3MgI were studied. A parallel reaction with free camphor was carried out.

To find out if the reactions proceeded in the normal way, that is with the formation of tertiary alkylborneols, we first used the bromination method, as according to S. S. Nametkin and M. A. Shlezinger [3] tertiary methylborneol readily dehydrates even under the effect of dilute acetic acid. We had hoped that the hydrogen bromide formed during the bromination of the Grignard reaction products would have a dehydrating effect on the tertiary alkylborneols, converting then into alkylcamphenes and bromination would proceed with noticeable bromine consumption. It was shown practically that camphor, borneol, isoborneol and some tertiary alcohols were brominated slightly in a carbon tetrachloride medium at 0° for 30 minutes, while at the same time reaction products of camphor and its complexes with methylmagnesium iodide and ethylmagnesium bromide underwent bromination with a considerably greater bromine consumption. Thus, by using the bromination method, we proved indirectly that, contrary to the statements of I. K. Sivkov and M. K. Matveeva [4] camphor reacts with ethylmagnesium bromide with the formation of tertiary ethylborneol.

As far as the effect of the preliminary conversion of camphor into complexes with the compositions (I), (II) and (III) on the course of the normal Grignard reaction was concerned, the complexes (I) and (II) somewhat lowered the yield of tertiary methylborneol and promoted its dehydration. Complex (III), on the contrary, notwithstanding the higher temperature at which the Grignard reaction took place, gave a product with approximately the same iodine number as that of the reaction product of camphor with ethylmagnesium bromide at a lower temperature (see Table 2). Consequently, as reported by V. M. Tolstopyatov, the complex formation is transformed into a factor with a known positive effect on the course of the normal Grignard reaction, at higher temperatures.

EXPERIMENTAL

Preparation of Complex Compounds of Camphor

Preparation of the complex $C_2H_5OMgI \cdot 2C_{10}H_{16}O$ (III). To 0.1 moles of C_2H_5OMgI in 60 ml of absolute ether, was added a solution of 0.4 moles of camphor* in 80 ml of absolute ether. After 12 hours, the precipitated product was quickly filtered off, carefully washed with absolute ether and, before analysis, kept for 24 hours in a vacuum desiccator over sulfuric acid.

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*All the experiments were carried out with racemic camphor with m.p. 175°.

Found %: Mg 4.56; I 22.78. $C_2H_5OMgI \cdot 2C_{10}H_{16}O$. Calculated %: Mg 4.61; I 22.50.

Preparation of the complexes $MgHal_2 \cdot 2C_{10}H_{16}O$ (I and II). To 0.1 moles of $MgBr_2 \cdot 2(C_2H_5)_2O$ was added a solution of 0.15 moles of camphor in 15 ml of absolute ether. The precipitate obtained was washed several times with absolute ether and kept 24 hours in a vacuum desiccator over sulfuric acid before analysis.*

Found %: Mg 4.55; Br 32.32. $MgBr_2 \cdot 2C_{10}H_{16}O$. Calculated %: Mg 4.97; Br 32.72.

To 0.1 moles of $MgI_2 \cdot 2(C_2H_5)_2O$ was added a solution of 0.15 moles of camphor in 15 ml of absolute ether. The precipitate obtained was washed several times with absolute ether and after drying was analyzed.

This complex was even decomposed by cold water to split out iodine and therefore it was analyzed quantitatively for ionic iodine and also for free iodine.

Found %: Mg 3.82; I^- 35.44; I 7.66. $MgI_2 \cdot 2C_{10}H_{16}O$. Calculated %: Mg 4.17; I 43.58.

The reaction of camphor and its complex compounds (I) and (II) with CH_3MgI. To 0.05 moles of camphor or 0.025 moles of the complexes (I) and (II), covered with 10 ml of absolute ether, was added 0.05 moles of CH_3MgI over 15 minutes. The reaction flasks were left to stand for 4 hours and then were heated for 18 hours at 36-38°. The course of the reaction was followed by measuring the volume of methane evolved.

TABLE 1

Data on the Reaction of Camphor and its Complex Compounds (I) and (II) with CH_3MgI

Starting material	Volume of methane evolved (NTP) (in ml)			Normal Grignard reaction (in % of theoretical)
	during the reaction with CH_3MgI	during the decomposition of the reaction product with water	during the decomposition of 0.05 moles of CH_3MgI with water (theoretical amount)	
Camphor	463	305	1120	31.4
$MgBr_2 \cdot 2C_{10}H_{16}O$(I)	487	360	1120	24.3
$MgI_2 \cdot 2C_{10}H_{16}O$(II)	480	409	1120	20.6

To prevent expansion of the ether vapor from interfering with the results, the lead to the gasometer passed through a spiral, cooled in solid carbon dioxide, and a Tishchenko bottle containing concentrated hydrochloric acid. The results of the experiments are given in Table 1.

The substances produced in the Grignard reactions were recovered in the usual way and after careful drying, were brominated.

The iodine numbers of the products obtained are given in Table 2.

Reaction of camphor with C_2H_5MgBr. To 0.2 moles of ethylmagnesium bromide, dissolved in 60 ml of absolute ether, was added a solution of 0.2 moles of camphor in 20 ml absolute ether over a period of 6 hours. The reaction was run at 15° with mechanical stirring. During the addition of the camphor and the 12 hour standing period, 1345 ml of gas (0° and 760 mm) was evolved, which contained 36.2 volume % (487 ml) of ethylene.

Assuming that the ethylene was formed as a result of the reduction of camphor to borneol by the reaction $C_{10}H_{16}O + C_2H_5MgBr \rightarrow C_{10}H_{17}OMgBr + C_2H_4$, the reduction reaction went to the extent of 10.8%.

The enolization reaction, calculated on the difference in the gas volumes (1345 ml minus 487 ml), amounted to 19.3%.

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* The complex was previously prepared by V. V. Chelintsev and N. M. Nazarova [5].

TABLE 2

Data on the Iodine Numbers of Camphor, the Products of the Reaction of its Complexes with Grignard Reagents, Borneol, Isoborneol and some Tertiary Alcohols.

Substance	Iodine number		
	total	substituted	added
Camphor	0.58	–	–
Borneol	2.87	0.44	2.43
Isoborneol	5.51	2.70	2.81
The reaction product of camphor with CH_3MgI	100.71	90.19	10.52
The reaction product of camphor with C_2H_5MgI	49.01	41.63	7.38
The reaction product of $MgBr_2 \cdot 2C_{10}H_{16}O$ with CH_3MgI	86.31	72.92	13.39
The reaction product of $MgI_2 \cdot 2C_{10}H_{16}O$ with CH_3MgI	82.15	65.58	16.57
The reaction product of $C_2H_5OMgI \cdot 2C_{10}H_{16}O$ with C_2H_5MgBr	48.77	39.75	9.02
Trimethylcarbinol	0.26	–	0.26
Dimethylethylcarbinol	1.43	0.65	0.78
Methylpropylisopropylcarbinol	3.52	3.20	0.32
Methylethylhexylcarbinol	2.46	0.41	2.05

The substance obtained from the Grignard reaction (30 g) was recovered by the usual method and melted completely at 155° and gave a positive Deniges reaction [6]. Data on the bromination of this material is given in Table 2.

Reaction of the complex compound (III) with C_2H_5MgBr. 0.2 moles of C_2H_5MgBr in 60 ml of absolute ether was added over a period of 4 hours to 0.1 moles of the complex (III) covered with 50 ml of absolute ether. During the addition of the Grignard reagent, 1400 ml of gas was evolved and during 6 hours heating at 36-38°, a further 1450 ml of gas. The whole 2850 ml of gas (0° and 760 mm) contained 28.0 volume % of ethylene. There was 17.8% of the reduction reaction and 45.8% of enolization reaction. The material from the Grignard reaction was recovered in the usual way and after drying weighed 30.5 g, melted completely at 155° and gave a positive Deniges reaction. Data on the bromination of it is given in Table 2.

The bromination of camphor, borneol, isoborneol, various tertiary alcohols and also the reaction products of camphor and its complex compounds (I), (II) and (III) with CH_3MgI and C_2H_5MgI was carried out by cooling a solution of a weighed sample in 10 ml of carbon tetrachloride down to 0°, adding 5 ml of a solution of bromine in carbon tetrachloride and allowing the solution to stand at 0° for 30 minutes. After the addition of KI solution and titration of excess iodine, the amount of HI was determined by reaction with KIO_3 [7]. The bromine solutions in carbon tetrachloride were prepared immediately before the iodine number determinations and from 16.65 to 20.06 ml of 0.1 N $Na_2S_2O_3$ solution was used in blank experiments on 5 ml of bromine solution in various experiments.

SUMMARY

1. It was shown that with MgI_2 and C_2H_5OMgI camphor formed complexes with the composition: $MgI_2 \cdot 2C_{10}H_{16}O$ and $C_2H_5OMgI \cdot 2C_{10}H_{16}O$.

2. The reactions of the complex compounds of camphor $MgBr_2 \cdot 2C_{10}H_{16}O$ (I), $MgI_2 \cdot 2C_{10}H_{16}O$ (II) and $C_2H_5OMgI \cdot 2C_{10}H_{16}O$ (III) with CH_3MgI and C_2H_5MgBr were studied and it was shown that (I) and (II) lowered the yield of tertiary methylborneol; complex (III), on the contrary, had a positive effect on the course of the normal Grignard reaction at higher temperature.

3. It was shown that bromination of the products of camphor and its complexes (I), (II), and (III) with organo-magnesium compounds could act as an indirect proof of the normal course of the Grignard reaction.

4. We demonstrated a characteristic of tertiary alkylborneols, namely their easy dehydration into alkylcamphene.

LITERATURE CITED

[1] V. I. Esafov and N. I. Novikov, J. Gen. Chem. 19, 1344 (1949)(T.p. 1343).*

[2] V. M. Tolstopyatov and B. N. Sverdlova, J. Gen. Chem. 2, 105 (1932).

[3] S. S. Nametkin and M. A. Shlezinger, J. Russ. Chem. Soc. 51, 144 (1919).

[4] I. K. Sivkov and M. K. Matveeva, J. Gen. Chem. 14, 319 (1944).

[5] V. V. Chelintsev and N. M. Nazarova, Bull. Soc. chim. (4), 41, 805 (1927).

[6] Deniges, Compt. rend. 126, 1043, 1277 (1898).

[7] McIlhiney, J. Am. Chem. Soc. 20, 1094 (1898); 21, 1087 (1899).

Received November 14, 1955

Ural State University

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* T.p = C. B. Translation pagination.

A CONTRIBUTION TO THE SYNTHESIS OF TERTIARY ALCOHOLS BASED ON CAMPHOR. III

V. I. Esafov and N. I. Novikov

The bromination method first used by us for the reaction products of camphor and its complex compounds with CH_3MgI and C_2H_5MgBr, turned out to be an indirect proof of the normal course of the Grignard reaction with the formation of tertiary alcohols – alkylborneols. The technical problem of isolating the individual compounds remained to be solved. To reduce the possibility of side reactions – enolization and reduction – to the minimum, all syntheses were carried out at low temperatures and with the reaction mixture considerably diluted by absolute ether. The crude products from the Grignard reaction were pressed out to separate the tertiary ethyl- and butylborneols. To remove the camphor, the liquid materials, rich in carbinols, were treated with semicarbazide by S. S. Nametkin's method as modified by us. The final carbinol purification was carried out by treating them with permanganate solution and steam distilling. To sum up, tertiary ethyl- and butylborneols in yields of 7% of theoretical for the former and 5% for the latter were obtained, contrary to data in the literature, by direct reaction of camphor with ethyl- and butylmagnesium bromides.*

EXPERIMENTAL

All syntheses were carried out with racemic camphor with m.p. 175°, semicarbazone – m.p. 236°.

Syntheses of tertiary ethyl- and butylborneol. The experiments were carried out in the apparatus illustrated in the figure. The ethyl- and butylmagnesium bromides were prepared in the flask A from 0.1 g-atoms of magnesium, 0.12 moles of the bromide and 60 ml of absolute ether. The Grignard reagent obtained was filtered through a Schott funnel, sealed to the flask, into the reaction jar where there was a solution of 0.1 moles of camphor in 65 ml of absolute ether cooled to − 15°. After shaking, the mixture was kept for 4 days at − 15°. In the same way three portions of camphor and Grignard reagent were subsequently introduced. The experiments took 16-25 days in all. The gas formed in the reaction was periodically let out. After several days a crystalline material formed and two liquid layers. These three products were separately decomposed with ice water and saturated ammonium chloride solution and then were worked up in the usual way. The data on the bromination of the substances obtained is given in the table.

For the isolation of the tertiary alcohols, we used only those products which had considerable iodine numbers. To isolate the tertiary ethylborneol, the product (18.5 g, see the table) was pressed at 150 kg/cm^2 in a special press with flannel filters. The liquid product from the press and the product from treating the flannel filters with ether in a Soxhlet extractor were combined with the liquid material from the lower ether layer (6 g, see the table). On an average, 12 g of liquid product was obtained from 0.4 moles of camphor. To separate the camphor from it, a solution of 8 g of semicarbazide hydrochloride and 8 g of crystalline sodium acetate in 32 ml of water was added to 16 g of the liquid product in 100 ml of alcohol and it was allowed to stand for 5 days at room temperature. The mixture obtained, containing a small precipitate of camphor semicarbazone, was neutralized with sodium bicarbonate to prevent dehydration of the ethylborneol by the dilute acetic acid and steam distilled. Distillation yielded 9 g of a colorless oil which was again treated with the corresponding amount of semicarbazide under the same conditions. In all we obtained 7.5 g of a colorless oil, which was purified from possible traces of dehydration product – ethylcamphene – by shaking continuously for 50 hours with a solution of 0.5 g of potassium permangante in 50 ml of water at 15° and then again steam distilling. The oil isolated (7 g) was dried with fused potash for 6 months. The yield of tertiary ethylborneol was 7%.

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* The formation of tertiary alkylborneols makes it convenient to obtain them in an optically active state.

Products	Yield (in g)	Sample for bromination (in g)	Number of ml of 0.1 N $Na_2S_2O_3$ solution		Iodine number*		
			Corresponding to the iodine from the sample	Consumed by iodine from the HI	total	substitution	addition
Syntheses with C_2H_5MgBr							
From the crystalline precipitate	32.5	0.1782	1.07	0.53	7.62	7.62	–
From the upper ether layer	18.5	0.2641	9.57	4.12	45.99	39.60	6.39
From the lower ether layer	6.0	0.2230	13.34	5.44	75.93	61.92	14.01
Syntheses with C_4H_9MgBr							
From the crystalline precipitate	41.5	0.2013	0.80	0.40	5.10	5.10	–
From the upper ether layer	8.5	0.2164	0.90	0.45	5.33	5.33	–
From the lower ether layer	6.0	0.2188	8.67	3.86	50.29	44.78	5.51

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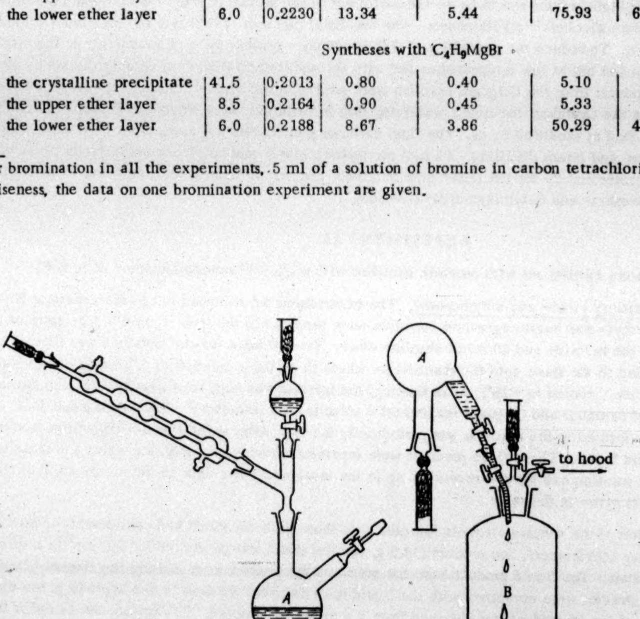
* For bromination in all the experiments, 5 ml of a solution of bromine in carbon tetrachloride was used. For conciseness, the data on one bromination experiment are given.



Apparatus for synthesis of tertiary ethyl- and butylborneols. Described in text.

Under precisely the same conditions we isolated and purified tertiary butylborneol, of which we obtained 4.2 g (5%) on an average from 0.4 moles of camphor.

Tertiary ethylborneol is a colorless liquid similar to glycerin, which boils at 223° with partial decomposition and at 67° (5 mm), is readily soluble in various organic solvents and has a weak stale, camphorish smell and a burning taste. It is readily volatile in air and steam:

d_4^{20} 0.9537, n_D^{20} 1.4815, MR_D 54.45. $C_{12}H_{22}O$. Calc. 54.74. Found %: C 78.80, 78.89; H 11.90, 12.17. Parachor 461.6. $C_{12}H_{22}O$. Calculated %: C 79.04; H 12.12. Parachor 468.4.

Tertiary butylborneol is a colorless, viscous liquid with b.p. 86° (5 mm) and with a very weak camphorish, but strongly stale smell:

d_4^{20} 0.9327, n_D^{20} 1.4795, MR_D 64.09. $C_{14}H_{26}O$. Calc. 63.98. Found %: C 79.82, 79.77; H 12.55, 12.44. Parachor 546.5. $C_{14}H_{26}O$. Calculated %: C 79.88; H 12.45. Parachor 546.4.

Preparation and analysis of phenylurethans of tertiary methyl-, ethyl- and butylborneols. a) A mixture of 3 g of methylborneol (m.p. 154-155°) and 3 g of phenylisocyanate was heated for 4 hours at 120°. After heating the mixture was allowed to stand for 18 hours. The product was dissolved in petroleum ether and filtered free from diphenylurea. The filtrate deposited shining, needle-like crystals of the phenylurethan, which were then recrystallized from petroleum ether. In all, we obtained 1.1 g of material with m.p. 138-139°. The nitrogen content of the methylborneol phenylurethan was determined by the Kjeldahl method, as modified by Esafov [3].

Found %: N 5.04. M 294.8 (Rast's method). $C_{18}H_{25}O_2N$. Calculated %: N 4.88. M 287.4.

b) A mixture which was composed of 3 g of ethylborneol and 3 g of phenylisocyanate was heated for 5 hours at 120°. After similar treatment, the reaction product yielded shining needle-like crystals of the phenylurethan with m.p. 119° amounting to 1.0 g.

Found %: N 4.51. M 306.9 (Rast's method). $C_{19}H_{27}O_2N$. Calculated %: N 4.64. M 301.4.

c) From a mixture of 3 g of butylborneol and 3 g of phenylisocyanate we obtained by the same processes 0.8 g of the phenylurethan as silky, white, needle-like crystals with m.p. 100-101°.

Found %: N 4.32. M 327.3 (Rast's method). $C_{21}H_{31}O_2N$. Calculated %: N 4.25. M 329.5

SUMMARY

1. It was proved that camphor reacts at low temperature with ethyl- and butylmagnesium bromide with the formation of tertiary alcohols – ethyl- and butylborneols.

2. For the first time racemic tertiary ethyl- and butylborneols and the corresponding phenylurethans were obtained.

LITERATURE CITED

[1] S. S. Nametkin and M. A. Shlezinger, J. Russ. Chem. Soc. 51, 144 (1919).

[2] S. S. Nametkin and A. I. Shavrygin, J. Gen. Chem. 3, 35 (1933); I. K. Sivkov and M. K. Matveeva, J. Gen. Chem. 14, 319 (1944).

[3] V. I. Esafov, J. Gen. Chem. 17, 1516 (1947).

Received November 14, 1955

Ural State University

THE SYNTHESIS OF COMPLEX ESTERS OF LIGNOCERIC ALCOHOL AND LIGNOCERIC ACID

A. M. Khaletsky and N. M. Gorskaya

In a previous paper [1] we showed that besides sterols, alcohols and acids of high molecular weight were also found among the products of alkaline hydrolysis of pine wood. A closer investigation of these showed that they consisted mainly of lignoceric alcohol and partly of lignoceric acid $CH_3-(CH_2)_{22}-CH_2OH$ and $CH_3-(CH_2)_{22}-COOH$. It seemed interesting to find out if the latter could be used for the synthesis of complex esters, suitable for replacing cocoa oil, wax and other fats.

References available in the literature on derivatives of lignoceric alcohol mention only the acetate, benzoate, phenacetate and its p-chloro- and p-bromo-derivatives; of the derivatives of lignoceric acid, the methyl, ethyl and phenyl esters had been synthesized [2]. The small amount of data on derivatives of lignoceric alcohol and acid is, probably, explained by the small amounts of the original material for investigation which were extracted from plant materials, such as beech, pine, plant oils etc. [3].

At the present time, as we had developed a method of isolating sterols and aliphatic alcohols from phytosterol-raw material, the availability of the latter made it possible to study in more detail the reactivity of lignoceric alcohol and acid. We obtained lignoceryl formate, acetate, oleate, oxalate, malonate and adipate by the esterification of lignoceric alcohol with organic acids. The lignoceric acid was obtained by oxidizing lignoceric alcohol [1]; when esterified with ethylene glycol it gave mono- and dilignoceric esters; when esterified with glycerin two materials were also obtained. The structures of the latter were not elucidated as it was not proved whether only the primary or also the secondary hydroxyl groups of the glycerin took part in the reaction. It should be noted that while lignoceric alcohol, especially when containing plant sterols, is capable of emulsifying fats, fatty oils and hydrocarbons (for example, vaseline oil), the complex esters synthesized by us did not have emulsifying properties.

EXPERIMENTAL

The complex esters from one mole of lignoceric alcohol (m.p. 74-76°) and 4 moles of organic acids – oleic, malonic and adipic – were synthesized by heating them in the presence of two moles of concentrated sulfuric acid for 10 hours. The acetic and oxalic esters were synthesized by heating lignoceric alcohol with acetic anhydride and anhydrous oxalic acid respectively; lignoceryl formate – by heating lignoceric alcohol with anhydrous sodium formate (2 moles) in the presence of sodium bisulfite for 10 hours. In Table 1 are described the conditions of the reactions, yields, elementary analysis data and also the melting points of the complex esters synthesized. They were all (with the exception of lignoceryl oleate) white crystalline materials, insoluble in water. Lignoceryl oleate was a waxy, slightly yellow mass.

The complex esters synthesized from one mole of lignoceric acid (m.p. 82-83°) and 4 moles of ethylene glycol and also glycerin, were prepared without the use of dehydrating materials by heating for 10 hours; they were slightly yellow, microcrystalline powders, insoluble in water and easily hydrolyzed by heating with alcoholic caustic potash. Table 2 gives the reaction conditions, yields, elementary analysis data and also the melting points of the complex esters of lignoceric acid.

SUMMARY

1. Complex esters were synthesized from lignoceric alcohol and organic acids (formic, acetic, oleic, oxalic, malonic and adipic) and their properties were described.

TABLE 1

Acylating agent	Esterification temperature	Crystallization	Melting point	Yield in %	Found (%)		Formula	Calculated %	
					C	H		C	H
Sodium formate	100°	From a mixture of acetone and chloroform (1 : 1)	57—59°	61.11	78.43, 78.86	13.05, 13.14	$C_{25}H_{50}O_2$	78.45	13.07
Acetic anhydride	100	From alcohol	55—57	98.30					
Oleic acid	100	From alcohol	44—48	79.00	81.40, 81.47	13.35, 13.30	$C_{42}H_{82}O_2$	81.50	13.36
Oxalic acid	185—190	From chloroform	81—82	81.86	78.61, 78.65	12.85, 12.91	$C_{50}H_{98}O_4$	78.66	12.95
Malonic acid	140	From chloroform	80—81	94.47	78.61, 78.63	12.95, 12.89	$C_{51}H_{100}O_4$	78.78	12.87
Adipic acid	155—160	From chloroform	79—80	56.77	78.93, 79.05	12.99, 13.01	$C_{54}H_{106}O_4$	79.13	12.94

TABLE 2

Alcohol	Esterification temperature	Crystallization	Melting point	Yield (in %)	Found (%)		Formula	Calculated (%)	
					C	H		C	H
Ethylene glycol	180°	From acetone	74—76°	44.21	78.63, 78.51	12.91, 12.90	$C_{50}H_{98}O_4$	78.66	12.95
		From chloroform	79—81	28.80	75.47, 75.55	12.69, 12.65	$C_{28}H_{52}O_3$	75.65	12.70
Glycerin	200	From acetone	73—75	24.32	77.10, 77.12	12.66, 12.67	$C_{51}H_{100}O_5$	77.19	12.71
		From chloroform	63—67	28.51	77.04, 77.15	12.96, 12.65	$C_{51}H_{100}O_5$	77.19	12.71

2. Complex esters were synthesized from lignoceric acid and ethylene glycol and also glycerin; furthermore, it was shown that ethylene glycol forms mono- and dilignoceric glycol esters, while glycerin forms isomeric dilignoceric esters.

LITERATURE CITED

[1] A. M. Khaletsky and N. N. Solomonik, J. Gen. Chem. 17, 1171 (1947); A. M. Khaletsky and I. M. Yurist, J. Gen. Chem. 24, 535 (1954) (T.p. 549).*

[2] O. Brunner and P. Wohl, Monatsh. 64, 21 (1934).

[3] P. Brigl and S. Fuchs, Z. Physiol. Chem. 119, 280 (1922).

Received November 2, 1955

Leningrad Chemical and Pharmaceutical Institute

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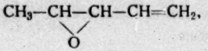
* T.p = C. B. Translation pagination.

ADDITION REACTIONS OF α-OXIDES OF PIPERYLENE

A. N. Pudovik and B. E. Ivanov

We were the first to obtain isomeric α-oxides of piperylene from piperylene chlorohydrin and by oxidizing piperylene with acetyl peroxide [1]. The reactions of piperylene oxides with water, acetic anhydride, acetyl chloride and ethyl alcohol are described in this article. The addition of water to α-oxides of piperylene takes place readily in the presence of small quantities of sulfuric acid. Glycols were separated in moderate yields which is explained by the difficulty and incompleteness of the separation from the reaction mixture. Penten-1-diol-3,4 (II) was obtained as the main reaction product of the hydration of 3,4-epoxypentene-1(I).

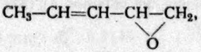


(I)

$CH_3CHOH{-}CHOH{-}CH{=}CH_2.$

(II)

The reaction with 1,2-epoxypentene-3 (III) proceeded analogously. Penten-3-diol-1,2 (IV) was obtained in 50% yield.



(III)

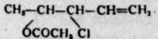
$CH_3{-}CH{=}CH{-}CHOH{-}CH_2OH.$

(IV)

Both reactions gave small amounts of higher-boiling fractions; it was impossible to separate products with a definite boiling point from them. Penten-3-diol-1,2 had been obtained earlier [2] by treatment of piperylene with hydrogen perioxide in an acetone solution.

Acetic anhydride adds to (I) and (III) with much more difficulty than water. Satisfactory results were obtained by heating a mixture of piperylene oxides with acetic anhydride at 140° in the presence of small amounts of boron trifluoride etherate. Penten-1-diol-3,4 diacetate was obtained from (I) and penten-3-diol-1,2 diacetate from (III).

Up to now the reactions of acid chlorides with oxides of diene hydrocarbons had not been studied. The reaction between acetyl chloride and (I) proceeded slowly at room temperature and considerably faster at 50-60°. 3-Chloropenten-1-ol-4 acetate (V) was obtained as the main reaction product. Its constants were identical with those of the acetylation product of 3-chloropenten-1-ol-4, which we obtained earlier by the addition of hypochlorous acid to piperylene [1].



$CH_3{-}\underset{OCOCH_3}{CH}{-}\underset{Cl}{CH}{-}CH{=}CH_2$

(V)

3-Chloropenten-1-ol-4 (V) does not undergo allyl regrouping in an acetic acid solution, containing a small amount of sulfuric acid, and this also confirm the structural formula assigned to it.

A small amount of a product with b.p. 125-126° (13 mm), corresponding to a mixed ester of chloropentenol and acetoxypentenol was separated from the higher boiling fraction, obtained in the reaction of (I) with acetyl chloride. The following formation scheme for it seemed to us to be the most probable. The small amount of hydrogen chloride in the acetyl chloride (formed by partial hydrolysis of acetyl chloride by atmospheric humidity) gave a chlorohydrin by reaction with (I) and this then added to (I); the addition product was acetylated by acetyl chloride. As a result a simple chloropentenol ester and pentendiol acetate were formed. Analysis for halogen and molecular refraction confirmed this hypothesis.

Addition of alcohol to divinyl oxide has been studied in detail [4-7]. In the presence of alkali metal alcoholates primary butendiol esters are formed exclusively or mainly, while in the presence of mineral acids – secondary ones are formed.

1-Ethoxypenten-3-ol-2, $CH_3-CH=CH-CHOH-CH_2OC_2H_5$ (VI) (92%), was isolated as a result of ethyl alcohol addition to (III) in the presence of sodium ethylate. A study of the saponification kinetics of ethoxychloropentene, obtained from (VI) by the action of phosgene, confirmed that the hydroxyl group in (VI) was in the allyl position. The chloroformic ester, formed in the first phase of the reaction, decomposed further when heated with a small amount of pyridine [5]. On the basis of the rather wide boiling range of ethoxychloropentene it seemed likely that its formation from 1-ethoxypenten-3-ol-2 was accompanied by allyl regrouping and, as a result, 1-ethoxy-2-chloropentene-3 was obtained in a mixture with the isomeric chloride.

By saponifying a 0.1 M aqueous-alcohol solution of ethoxychloropentene, it was established that 67% of it was saponified in 4 hours at 50°. The facility of the saponification proved that the chlorine atom in it was in the allyl position. The saponification of 1-methoxy-5-chloropentene-3, which has chlorine in the allyl position, and of glycol chlorohydrin carried out under analogous conditions for comparison, showed that they were 60.1 and 2.7% saponified respectively.

The action of ethyl alcohol on the oxide (III), in the presence of sulfuric acid, resulted in tar production; no individual products could be isolated from the reaction mixture.

EXPERIMENTAL

Addition of water to 3,4-epoxypentene-1 (I). A drop of sulfuric acid was added to 25 ml of distilled water followed by the gradual addition of 10 g of (I). As a considerable amount of heat was evolved, the reaction flask was cooled in ice water during the reaction. After half an hour of stirring, the reaction was complete. The aqueous solution was saturated with salt and extracted several times with ether and then with chloroform. After distilling off the solvents and twice distilling the residue with a small column, we obtained 4 g (42%) of penten-1-diol-3,4 (II) and also small amounts of lower and higher boiling fractions.

B.p. 93-94° (20 mm), d_4^{20} 1.0091, n_D^{20} 1.4565, MR_D 27.48; calc. 27.87. Found %: C 58.96; H 9.90. $C_5H_{10}O_2$. Calculated %: C 58.82; H 9.80.

Penten-1-diol-3,4 is a thick, viscous liquid, which is readily soluble in water and alcohol and difficultly soluble in ether and chloroform. It was not possible to isolate a single substance by repeated distillation of the fraction with b.p. 94-118° (20 mm) (2 g).

Addition of water to 1,2-epoxypentene-3 (III). The reaction was carried out with the same quantities and in the same way as described in the previous experiment. As a result of two distillations, we obtained 6 g of penten-3-diol-1,2 (IV) and also small amounts of lower and higher boiling fractions.

B.p. 109-110° (20 mm), d_4^{20} 1.0200, n_D^{20} 1.4690, MR_D 27.83; calc. 27.87. Found %: C 58.70; H 9.90. $C_5H_{10}O_2$. Calculated %: C 58.82; H 9.80.

We tried to increase the yield of the glycols by isolating them from the aqueous solution by distillation in vacuum. However, we observed gradual decomposition of the residue during the distillation; we were not able to isolate the glycol in a pure form.

Reaction of 3,4-epoxypentene-1 (I) with acetic anhydride. 15 g of (I), 30 g of acetic anhydride and 0.2 g of boron trifluoride etherate were heated at 140° for 10 hours. After distillation in vacuum with a Widmer fractionating column, we obtained 5 g (22%) of the diacetate of penten-1-diol-3,4.

B.p. 99-100° (20 mm), d_4^{20} 1.0272, n_D^{20} 1.4292, MR_D 46.68; calc. 46.60. Found %: C 57.96; H 7.54. $C_9H_{14}O_4$. Calculated %: C 58.07; H 7.55.

The diacetate of penten-1-diol-3,4 is a colorless liquid with a pleasant ester smell; it is soluble in ether, alcohol and chloroform.

Reaction of 1,2-epoxypentene-3 (III) with acetic anhydride. 0.2 ml of boron trifluoride etherate was added to 15 g of (III) and 30 g of acetic anhydride. Considerable evolution of heat was observed. The reaction mixture was heated at 90-100° for 4 hours and then distilled. We obtained 13 g (56%) of the diacetate of penten-3-diol-1,2, about 6 g of a lower boiling fraction and 4 g of undistillable residue.

B.p. 116-117° (20 mm) d_4^{20} 1.0425, n_D^{20} 1.4380, MR_D 46.83; calc. 46.60. Found %: C 57.86; H 7.34. $C_9H_{14}O_4$. Calculated %: C 58.07; H 7.55.

Action of acetyl chloride on 3,4-epoxypentene-1 (I). A mixture of 56 g of acetyl chloride and 50 g of (I) was heated on a water bath at 50-60° for 4 hours. After treatment with water, the ester was extracted by distillation of the reaction products with a Widmer fractionating column. After two distillations, we obtained 27 g of the acetate of 3-chloropenten-1-ol-4 (V).

B.p. 65-66° (13 mm), d_4^{20} 1.0604, n_D^{20} 1.4400, MR_D 40.38; calc. 40.61. Found %: Cl 22.18. $C_7H_{11}O_2Cl$. Calculated %: Cl 21.80.

By distillation of the higher boiling fraction, we obtained 5 g of the mixed ester of chloropentenol and acetoxypentenol.

B.p. 125-126° (13 mm), d_4^{20} 1.0358, n_D^{20} 1.4572, MR_D 64.84; calc. 64.84. Found %: Cl 14.05. $C_{12}H_{19}O_3Cl$. Calculated %: Cl 14.40

Experiments on the isomerization of the diacetate of penten-3-diol-1,2 and the acetate of 3-chloropenten-1-ol-4 in acetic acid solution in the presence of sulfuric acid and copper sulfate (room temperature and 5 days), did not give positive results.

Addition of ethyl alcohol to 1,2-epoxypentene-3 (III) in the presence of sodium ethylate. 0.5 g of sodium was dissolved in 120 ml of anhydrous ethyl alcohol and then 17.5 g of (III) was added. The reaction mixture was heated on a water bath at 80-90° for 10 hours. We obtained 25 g of 1-ethoxypenten-3-ol-2 (VI).

B.p. 67-68° (13 mm); d_4^{20} 0.9146, n_D^{20} 1.4395, MR_D 37.42; calc. 37.23. Found %: C 64.10; H 10.91; OH 12.78. $C_7H_{14}O_2$. Calculated %: C 64.62; H 10.77; OH 13.07.

The lower boiling fraction was 2.5 g and the residue about 3 g.

Action of phosgene on 1-ethoxypenten-3-ol-2 (VI). A stream of dry phosgene was passed through 15 g of 1-ethoxypenten-3-ol-2 until 12 g had been taken up. On the addition of 1 g of pyridine to the reaction mixture, a considerable evolution of carbon dioxide began. The reaction mixture was heated at 110-120° for 2 hours and then distilled in vacuum. We obtained 5 g of a product, boiling over a quite wide temperature interval.

B.p. 64-72° (12 mm) d_4^{20} 1.0617, n_D^{20} 1.4525. Found %: Cl 22.89. $C_7H_{13}OCl$. Calculated %: Cl 23.91.

The chloride was hydrolyzed at 50° in 50% aqueous alcohol solution. The rate of hydrolysis was determined in separate experiments by the concentration of chloride ion (Volhard titration). After 4 hours, the chloride was 67% hydrolyzed.

SUMMARY

1. The addition of water to 3,4-epoxypentene-1 and 1,2-epoxypentene-3 was studied. Penten-1-diol-3,4 and penten-3-diol-1,2 were obtained and characterized.

2. By the reaction of acetic anhydride with 3,4-epoxypentene-1, penten-2-diol-3-4 diacetate was obtained, while with 1,2-epoxypentene-3 – penten-1-diol-3,4 diacetate.

3. The addition of acetyl chloride to 3,4-epoxypentene-1 was studied. 3-Chloropenten-1-ol-4 acetate was obtained and characterized.

4. 1-Ethoxypenten-3-ol-2 was obtained by the action of ethyl alcohol on 1,2-epoxypentene-3 in the presence of sodium ethylate.

LITERATURE CITED

[1] A. N. Pudovik and B. E. Ivanov, Proc. Acad. Sci. USSR 103, 443 (1955).

[2] P. Seguim, Compt. rend. 216, 667 (1943).

[3] W. Oroshnik and R. Mallory, J. Am. Chem. Soc. 72, 4608 (1950).

[4] A. A. Petrov, J. Gen. Chem. 8, 131 (1938); 16, 1625 (1946).

[5] R. Kadesh, J. Am. Chem. Soc. 68, 141 (1946).

[6] P. Bartlett and S. Ross, J. Am. Chem. Soc. 70, 926 (1948).

[7] D. Swern, G. Billen and H. Knight, J. Am. Chem. Soc. 71, 1152 (1949).

Received October 31, 1955

Kazan State University

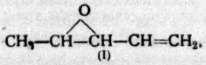
OXIDATION OF DIVINYL, ISOPRENE AND PIPERYLENE WITH ACETYL PEROXIDE

A. N. Pudovik and B. E. Ivanov

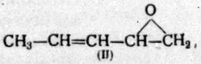
Pummerer and Reindel [1] obtained divinyl oxide by oxidizing divinyl with benzoyl peroxide. Also, according to their data, isoprene oxidation takes place at the substituted double bond with the formation of 2-methyl-1,2-epoxybutene-3. A. A. Petrov [2], who synthesized 2-methyl-1,2-epoxybutene-3 by splitting out hydrogen bromide from 2-methyl-1-bromobuten-3-ol-2, considered that Pummerer and Reindel obtained a mixture of two isomeric isoprene α-oxides. Boseken [3] obtain a glycol monoacetate from acetyl peroxide treatment of isoprene in an acetic acid solution and then by saponification obtained 2-methylbuten-3-diol-1,2. The synthesis of diene hydrocarbon dioxides is described in [4,5]. Oxidation of piperylene with the peroxides of organic acids had not been studied at all up to now.

We studied the oxidation of divinyl, isoprene and piperylene with acetyl peroxide in a 3% ether solution. The results for divinyl and isoprene turned out to be analogous to those obtained earlier with benzoyl peroxide. Divinyl oxide was obtained in a yield of 50% by oxidation of divinyl. Isoprene was oxidized in a considerably larger amount than in Pummerer and Reindel's experiments; 2-methyl-1,2-epoxybutene-3 was obtained in 42% yield. There was a very insignificant amount (3%) of a higher-boiling fraction and no individual products could be separated from it.

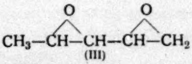
99% piperylene with a content of approximately 70% of the trans-form was used for oxidation. As a result of the oxidation a mixture of piperylene monoxides was obtained: 3,4-epoxypentene-1 (I) and 1,2-epoxypentene-3 (II) in a total yield of 58%:


$\mathrm{CH_3{-}\overbrace{CH{-}CH}^{O}{-}CH{=}CH_2}$,

(I)


$\mathrm{CH_3{-}CH{=}CH{-}\overbrace{CH{-}CH_2}^{O}}$,

(II)


$\mathrm{CH_3{-}\overbrace{CH{-}CH}^{O}{-}\overbrace{CH{-}CH_2}^{O}}$

(III)

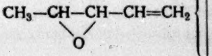
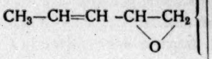
55% of the isomer mixture consisted of (I). (I) and (II) were identified by comparing their constants with those of the α-oxides, obtained by us earlier from piperylene chlorohydrins [6]. The rather wide boiling range of piperylene α-oxides, obtained by piperylene oxidation, is quite noticeable. This is explained by the fact that both piperylene α-oxides are mixtures of geometric isomers. The residue (of about 12%) left after distilling the α-oxides, boiled in the range 120-180°, and no individual products could be separated from it. Piperylene oxidation was carried out in 8 and 20% solutions of acetyl peroxide. With all other conditions equal, the yield of mixtures of (I) and (II) decreased in these experiments to 37 and 12% respectively. The amount of higher-boiling products increased sharply.

Beside the yield, the ratio of α-oxides changed considerably. 55% of the isomer mixture was oxide (I) when the oxidation was carried out with 3% acetyl peroxide, while it was approximately 100% when 20% acetyl peroxide was used. This shows the considerably greater reactivity of oxide (II) in comparison with (I) and its conversion in the reaction into secondary products: pentendiol monoacetates, piperylene dioxide and reaction products of the dioxide with acetic acid.

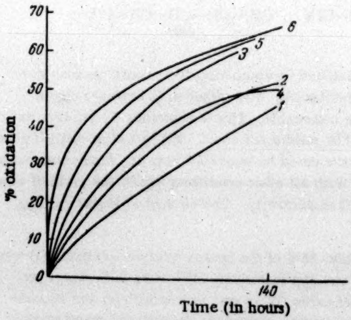
Piperylene oxidation to the dioxide was carried out in a 5% ether solution of acetyl peroxide. Beside the large quantity of monoxides and higher-boiling products, piperylene dioxide (III) was obtained in a yield of approximately 12%.

We carried out acetyl peroxide oxidation of piperylene in the cis- (100%) and trans-forms (92%) to obtain individual piperylene α-oxides. On the basis of the paper by Witnauer and Swern [7] who show that cis-oxides are obtained by oxidizing the cis-olefin series with acetyl and benzoyl peroxides, while by oxidizing trans-olefins, trans-oxides are obtained, we considered that this tendency would be maintained in the oxidation of stereoisomeric diene hydrocarbons. Actually, in each case of the oxidation of the cis- and trans-forms of piperylene both α-oxides were obtained with rather narrow boiling points and greatly differing constants; the values of the constants of the α-oxides obtained from technical piperylene (mixture of cis and trans-forms) lie between them. As was expected (see table), cis-oxides, obtained from cis-piperylene, had a higher boiling point, refractive index and specific gravity than the trans-oxides obtained from the trans-form of piperylene.

However, it was still impossible to come to definite conclusions on the structure of the cis- and trans-piperylene oxides obtained, as it was possible that they consisted of a mixture of stereoisomers, whose stereoisomerism depended on the different steric position of the oxide ring substituent.

Formula	Method of preparation	Temperature of boiling point	d_4^{20}	n_D^{20}
 $CH_3-\underset{O}{CH-CH}-CH=CH_2$	From chlorohydrin	82 — 83°	0.8464	1.4132
	Oxidation of cis- and trans- mixture	82 — 86	0.8472	1.4140
	Oxidation of the cis-form	84.5— 86	0.8592	1.4182
	Oxidation of the trans-form (92%)	82 — 83.5	0.8432	1.4110
 $CH_3-CH=CH-\underset{O}{CH-CH_2}$	From chlorohydrin	103 —104	0.8750	1.4345
	Oxidation of cis- and trans-mixture	102 —105	0.8752	1.4355
	Oxidation of the cis-form	103 —104	0.8953	1.4385
	Oxidation of the trans-form	101 —102	0.8720	1.4325

The kinetics of the oxidation of divinyl, isoprene, cis- and trans-piperylenes, 2,3-dimethylbutadiene-1,3 and hexadiene-2,4 with 3% solution of acetyl peroxide in an ether solution were studied to find out the relation of the oxidation rate of diene hydrocarbons to their structure. The results obtained are shown in the graph.



The relation of the oxidation rate of diene hydrocarbons to their structure. 1) Divinyl; 2) isoprene; 3) trans-piperylene; 4) cis-piperylene; 5) dimethylbutadiene; 6) hexadiene.

The diene hydrocarbons may be arranged in the following series according to their increasing oxidation rate: divinyl < isoprene < cis-piperylene < trans-piperylene < 2,3-dimethylbutadiene-1,3 < hexadiene-2,4. As can be seen, the accumulation of methyl groups in the diene system facilitates the oxidation process; the substitution of hydrogen atoms in the divinyl molecule by methyl groups on the outer carbon atoms accelerates oxidation to a greater degree than substitution on the center ones. It is likewise interesting to note that the considerable difference in the reaction rates in diene synthesis, observed with geometric isomers of diene hydrocarbons, appears to be much less in oxidations with acetyl peroxide. Cis-piperylene is oxidized somewhat slower than trans-piperylene.

EXPERIMENTAL

Oxidation of divinyl with acetyl peroxide. To a solution of 60 g of divinyl in 2 liters of anhydrous ether was added 80 ml of 90% acetyl peroxide. The reaction mixture was allowed to stand at room temperature. The reaction was followed by testing samples with potassiumiodide. The reaction was almost complete after 15 days. The acetic acid was neutralized with 10% caustic soda solution. The ether solution was dried with sodium sulfate. After distilling off the ether, the residue was distilled on a bubble-cap column with an efficiency of 10 theoretical plates. We obtained 35 g of divinyl oxide.

B. p. 66-66.5°, d_4^{20} 0.8720, n_D^{20} 1.4105.

Oxidation of isoprene with acetyl peroxide. 110 g of isoprene in 4 liters of anhydrous ether was oxidized with 128 ml of 95% acetyl peroxide. The reaction was almost complete after 12 days. We obtained 55 g of 1,2-epoxy-2-methylbutene-1.

B. p. 79.5-80.5°, d_4^{20} 0.8574, n_D^{20} 1.4180.

Oxidation of a mixture of cis- and trans-piperylene with acetyl peroxide. To 170 g of piperylene (99%, n_D^{20} 1.4320) in 6 liters of anhydrous ether was added 200 ml of 80% acetyl peroxide. The reaction was almost complete after 9 days. Distillation of the oxides was carried out on a bubble-cap column with an efficiency of 20 theoretical plates. After two distillations we isolated 45 g of a mixture of cis- and trans-3,4-epoxypentene-1 (I) and 34 g of a mixture of cis- and trans-1,2-epoxypentene-3 (II).

(I): b.p. 82-86°, d_4^{20} 0.8472, n_D^{20} 1.4140. Found %: C 71.15; H 9.56. C_5H_8O. Calculated %: C 71.43; H 9.52.
(II): b. p. 102-105°, d_4^{20} 0.8752, n_D^{20} 1.4355. Found %: C 71.85; H 9.78. C_5H_8O. Calculated %: C 71.43; H 9.52.

The residue from the distillation (15 g) distilled in the range 120-180°.

In a repeat experiment 68 g of piperylene in 1 liter of ether was oxidized with 86 ml of 90% acetyl peroxide. The reaction was accompanied by heating up of the reaction mixture; it was complete after 5 days. We obtained 21 g of (I) and 10 g of (II). On further lowering the amount of ether the reaction proceeded even more vigorously; the yield of oxides fell and the amount of high boiling residue increased.

Oxidation of cis-piperylene with acetyl peroxide. The cis-piperylene was obtained by treating technical piperylene twice with maleic anhydride. (Heating and mixing – for 8 hours). 78 g of cis-piperylene (n_D^{20} 1.4358) in 3 liters of ether was oxidized with 90 ml of 85% acetyl peroxide. The reaction was complete after 10 days. We obtained 20 g of cis-3,4-epoxypentene-1 (I) and 14 g of cis-1,2-epoxypentene-3 (II).

(I cis): b.p. 84.5-86°, d_4^{20} 0.8592, n_D^{20} 1.4182. Found %: C 71.20; H 9.74. C_5H_8O. Calculated %: C 71.43; H 9.52.
(II cis): b.p. 103-104°, d_4^{20} 0.8953, n_D^{20} 1.4385. Found %: C 71.00; H 9.48. C_5H_8O. Calculated %: C 71.43; H 9.52.

Oxidation of trans-piperylene with acetyl peroxide. To prepare the trans-piperylene, technical piperylene was heated for 12 hours with iodine and picric acid. For the oxidation we used piperylene containing 92% of the trans-form (b.p. 41-42°, n_D^{20} 1.4308). 70 g of trans-piperylene in 3 liters of anhydrous ether was oxidized with 85 ml of 93% acetyl peroxide. The reaction was complete after 8 days. After working up and distilling the reaction mixture twice through a column with an efficiency of 10 theoretical plates, we obtained 20 g of trans-3,4-epoxypentene-1 (I) and 15 g of trans-1,2-epoxypentene-3 (II).

(I trans): b.p. 82-83.5°, d_4^{20} 0.8432, n_D^{20} 1.4110. Found %: C 71.31; H 9.55. C_5H_8O. Calculated %: C 71.43; H 9.52.
(II trans): b.p. 101-102°, d_4^{20} 0.8720, n_D^{20} 1.4325. Found %: C 71.20; H 9.6. C_5H_8O. Calculated %: C 71.43; H 9.52.

Synthesis of piperylene dioxide (III). 190 ml of 85% acetyl peroxide was added to 68 g of piperylene in 4 liters of anhydrous ether. The reaction was almost complete after 17 days. After several distillations of the reaction mixture, we isolated 12 g of 3,4-epoxypentene-1, 7 g of 1,2-epoxypentene-3 and 7 g of piperylene dioxide:

B. p. 56-57° (20 mm), d_4^{20} 1.0278, n_D^{20} 1.4295, MR_D 25.1; calc. 24.17. Found %: C 59.48; H 8.14. $C_5H_8O_2$. Calculated %: C 60.00; H 8.00.

Piperylene dioxide is a colorless liquid, which is readily soluble in alcohol and ether and insoluble in water. On standing it becomes yellow.

Kinetics of the acetyl peroxide oxidation of diene hydrocarbons. 0.4 M solutions of divinyl, isoprene, cis- and trans-piperylene, dimethylbutadiene and hexadiene in anhydrous ether were oxidized with acetyl peroxide (3%) at 17-18°. After every 18-20 hours, 5 ml samples of the reaction mixtures were taken and added to 2% potassium iodide solution. The iodine liberated was quickly titrated with 0.1 N hyposulfite solution. The results obtained are shown in the figure.

SUMMARY

1. The α-oxide of divinyl and the α-oxide of isoprene (2-methyl-1,2-epoxybutene-3) were obtained in yields of 50 and 42% respectively by oxidizing divinyl and isoprene with acetyl peroxide in an ether solution.

2. By oxidizing piperylene with acetyl peroxide we obtained both isomeric α-oxides: 3,4-epoxypentene-1 and 1,2-epoxypentene-3, in a total yield of 58%. The isomer mixture contained 55% of the former. The oxidation of cis- and trans-forms of piperylene was studied. Cis- and trans-piperylene oxides were isolated and characterized.

3. The diene hydrocarbons may be arranged according to the increasing oxidation rate in the following series: divinyl < isoprene < cis-piperylene < trans-piperylene < 2,3-dimethylbutadiene-1,3 < hexadiene-2,4. The accumulation of methyl groups at the outer carbon atoms in a divinyl molecule accelerates the oxidation process to a greater degree than substitution at the center ones.

LITERATURE CITED

[1] Pummerer and Reindel, Ber. 66, 335 (1935).

[2] A. A. Petrov, J. Gen. Chem. 13, 481 (1943).

[3] J. Boseken, Rec. trav. chim. 54, 657 (1935).

[4] Everett and Kon, J. Chem. Soc. 1950, 3131.

[5] V. I. Pansevich-Kolyada, G. S. Strigalova and Z. B. Idelchik, J. Gen. Chem., Supple. II, 1418 (1953).

[6] A. N. Pudovik and B. E. Ivanov, Proc. Acad. Sci. USSR 103, 443 (1955).

[7] D. Swern and Witnauer, J. Am. Chem. Soc. 72, 3364 (1950).

Received October 31, 1955

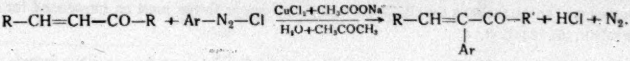
Kazan State University

HALOGENATION OF UNSATURATED COMPOUNDS WITH AROMATIC DIAZO COMPOUNDS

I. THE REACTION OF PHENYLDIAZONIUM CHLORIDE AND BROMIDE WITH BUTADIENE-1,3 AND SOME REACTIONS OF 4-CHLORO-1-PHENYLBUTENE-2

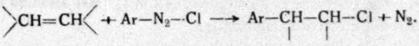
A. V. Dombrovsky and A. P. Terentyev

K. Meyer et al. [1] were the first to note that isoprene reacted with aromatic diazonium salts in the cold and in an acidic medium with the formation of a nitrogen-containing material. K. Meyer [2] investigated this reaction as applied to mono- and diolefins and came to the conclusion that azo combination took place: with p-nitrophenyldiazonium, conjugated dienes form a well-crystallized colored azo compound; monoolefins do not react. A. P. Terentyev and A. A. Demidova [3] confirmed the fact that only conjugated dienes undergo azo combination. A. P. Terentyev [4] proposed a reaction with diazonium salts for the qualitative and quantitative determination of conjugated dienes. Meerwein et al. [5] described a reaction of aromatic diazonium salts with α,β-unsaturated carbonyl compounds, resulting in the formation of aryl substituted compounds according to the general scheme:



$$R{-}CH{=}CH{-}CO{-}R + Ar{-}N_2{-}Cl \xrightarrow[H_2O+CH_3COCH_3]{CuCl_2+CH_3COONa} R{-}CH{=}\underset{\substack{|\\ Ar}}{C}{-}CO{-}R' + HCl + N_2.$$

Besides the vinyl arylation, diazonium salt addition occurred at the multiple bond:



$$>CH{=}CH< + Ar{-}N_2{-}Cl \longrightarrow Ar{-}\underset{|}{C}H{-}\underset{|}{C}H{-}Cl + N_2.$$

In this work we describe the reaction of phenyldiazonium chloride and bromide with butadiene-1,3 and examine the role of those factors that promote the formation of 4-halogeno-1-phenylbutene-2:

$$C_6H_5{-}N_2{-}Hal + CH_2{=}CH{-}CH{=}CH_2 \xrightarrow[\text{где Hal=Cl, Br.}]{} C_6H_5{-}CH_2{-}CH{=}CH{-}CH_2Hal + N_2,$$

Sodium acetate was introduced as buffer into the reaction mixture of the Meerwein reaction between unsaturated compounds and diazonium salts. Our experiments showed that without sodium acetate the yield of 4-chloro-1-phenylbutene-2 (I) was only 24% based on aniline, in the reaction of phenyldiazonium chloride with divinyl in a water-acetone solution in the presence of cupric chloride. Chlorobenzene and phenol were the main reaction products. The yield of (I) increased to 50% by carrying out the reaction in an acetate buffer, but a considerable amount of tar was formed. We carried out a series of experiments, substituting the sodium acetate by other materials, and, as can be seen from the table, the best results were obtained with calcium oxide; furthermore, the reaction in this case proceeded at 6-8°, while with sodium acetate at 18-20°.

The nature of the solvent used also affected the course of the reaction. The best results were obtained when the reaction was carried out in a water-acetone solution (1:1). In certain cases, for example in halogenoarylation of maleic acid [6], acetone was not used at all, as both components dissolved satisfactorily in water.

The Relation of the Product Yields in the Reaction between Phenyldiazonium Chloride and Divinyl to Additives

Additives	Yield (in %)					
	$C_6H_5CH_2-CH=CH-CH_2-Cl$	C_6H_5Cl	C_6H_5OH	C_6H_6	Chloro-acetone	Tars
CaO	70	7	—	Traces	Traces	10.7
MgO	60	17.7	2.6	"	"	16.5
CH_3COONa	50	18	5.3	"	"	22.2
Without additives . .	24	30	30	"	"	7.8
$Al(OH)_3$	12	35.6	42.5	—	—	5
CuO	11	74	—	—	—	6.3
ZuO	0	32	25	9	—	30

Acetone also had a definite specific effect on the direction of the reaction. This is doubtlessly due to the mechanism of the reaction between unsaturated molecules of the organic material, on the one hand, and diazonium salt ions, on the other. The existence of the latter in the ionic form is closely connected with the reaction medium, the solvent. The dielectric constant and the size of the dipole moment are the most important of the physical properties of the solvent. In contrast to other solvents, acetone has a relatively large dielectric constant and a large dipole moment. Such solvents as pyridine and dioxane, although they are completely miscible with water, have small values for these constants. Alcohols have high constants but they themselves enter into chemical reaction with aryldiazonium salts. Acetonitrile was tested by Meerwein [5] and gave good results, which fully agree with our reasoning. The availability of acetone made it most suitable as the solvent for this reaction.

The presence of a catalyst, cupric chloride or cupric bromide, was a necessary condition for carrying out halogenoarylation. We established that 0.20-0.23 moles of cupric halide must be introduced for each mole of diazonium salt in the reaction.

Hodgson et al.[7] interpreted the catalytic action of the Cu^{++} ion (and some other metals, for example $AlCl_3$, $FeCl_3$) as confirming that in the decomposition of diazo compounds the electrophilic diazo cation $Ar-\overset{+}{N}\equiv N$ reacts with the anionic halogen, entering into the composition of the complex formed by halogen ions and the catalytic action of the salt. The existence of a complex ion $CuCl_4^-$ was assumed in the case of divalent copper, although Waters [8] considered it inactive catalytically.

The problem of the reaction mechanism of arylation and halogenoarylation of unsaturated compounds is still not clear. Meerwein [5] proposed an ionic mechanism according to which aryl cations were formed by diazonium salt decomposition and reacted at the multiple bond of the unsaturated molecule. However, such an explanation contradicts the experimental data of Meerwein himself and of other authors. Coelsch and Boekelheide [9] thought that the process proceeded through a stage of free radical formation, and assumed that aryldiazonium salts in the presence of acetic acid buffer were converted into arylazoacetates which decomposed into free radicals. But even this interpretation does not explain the cases of reaction without sodium acetate additions, for example, in a hydrochloric acid medium [10], or, as was shown by us, in the presence of lime, magnesium oxide etc.

A. N. Nesmeyanov and his school [11, 12] studied the decomposition mechanism of aromatic diazocompounds and their double salts. The diazonium salts may decompose in solutions either homolytically with free radical formation or heterolytically with formation of particles of ionic character, depending on the reaction conditions and nature of the anions. Taking this into consideration as well as the capacity of aromatic diazonium salts to form complex compounds, we think that first the complex $C_6H_5-N_2-Cl\cdot CuCl_2$ is formed, which under the conditions of a buffer or neutral medium is converted from an ionic to an unstable compound, with a homopolar type of structure, which easily undergoes homolytic decomposition into an aryl radical and atomic chlorine which react in several directions – with the unsaturated molecules, solvent or with each other by the scheme:

$$[C_6H_5-N_2]^+Cl^- + CuCl_2 \longrightarrow C_6H_5-H_2-Cl\cdot CuCl_2 \rightleftharpoons C_6C_5-N_2-CuCl_3,$$

$$[C_6H_5-N_2]^+CuCl_3^- \rightleftharpoons C_6H_5\vdots N{=}N\vdots CuCl_3 \longrightarrow C_6H_5\cdot + Cl\cdot + CuCl_2 + N_2,$$

$$C_6H_5\cdot + Cl\cdot + CH_2{=}CH-CH{=}CH_2 \longrightarrow C_6H_5-CH_2-CH{=}CH-CH_2Cl.$$

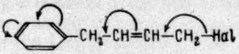
Side reactions:

$$C_6H_5\cdot + Cl\cdot \longrightarrow C_6H_5Cl,$$
$$C_6H_5\cdot + CH_3-CO-CH_3 \longrightarrow C_6H_6,$$
$$Cl\cdot + CH_3-CO-CH_3 \longrightarrow CH_3-CO-CH_2-Cl,$$
$$C_6H_5N_2^+ + H_2O \longrightarrow C_6H_5OH.$$

It becomes clear from this why only cupric halides acted as catalysts in this reaction, while sulfates and nitrates were inactive, as the formation of the radicals $SO_4\cdot$ or $NO_3\cdot$ is improbable.

The reaction between phenyldiazonium bromide and divinyl in the presence of magnesium oxide and $CuBr_2$ proceeded extremely energetically; however, the main reaction product was bromobenzene (56%) and 4-bromo-1-phenylbutene-2 was obtained in only 33% yield. This compound was synthesized by a Grignard reaction from phenylmagnesium bromide and 1,4-dibromobutene-2 [13].

Compounds obtained by divinyl halogenoarylation contained halogen in the allyl position and its lability was still more increased by the presence of a phenyl radical in the conjugated position.



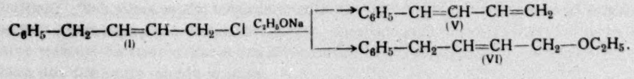
4-Chloro-1-phenylbutene-2 (I) was obtained only in 1948 by the reaction of thionyl chloride with 1-phenylbuten-2-ol-4, which was synthesized, in its turn, from 3,4-epoxybutene-1 and phenylmagnesium bromide [14].

We studied a series of reactions in which 4-chloro-1-phenylbutene-2 took part. The oxidation of (I) resulted in benzoic acid:

$$C_6H_5-CH_2-CH{=}CH-CH_2Cl \xrightarrow[KMnO_4;K_2Cr_2O_7]{+O} C_6H_5COOH.$$

4-Bromo-1-phenylbutene-2 was formed by heating (I) with an excess of potassium bromide in acetone. The exchange of chlorine for iodine proceeded readily by boiling (I) with potassium iodide in alcohol. Chlorine was just as readily exchanged for a thiocyanide group. (I) reacted smoothly with diethylamine giving 4-diethylamino-1-phenylbutene-2 in almost quantitative yield.

The reaction of (I) with an alcohol solution of sodium ethylate resulted in the formation of two materials in almost equal amounts – 1-phenylbutadiene-1,3 and 1-phenyl-4-ethoxybutene-2:



$$\underset{(I)}{C_6H_5-CH_2-CH{=}CH-CH_2-Cl} \xrightarrow{C_2H_5ONa} \begin{cases} \longrightarrow \underset{(V)}{C_6H_5-CH{=}CH-CH{=}CH_2} \\ \longrightarrow \underset{(VI)}{C_6H_5-CH_2-CH{=}CH-CH_2-OC_2H_5}. \end{cases}$$

(I) reacted quantitatively with dioxane dibromide in the cold and was converted into 1-phenyl-4-chloro-2,3-dibromobutane. (I) reacted in the usual manner with phenylmagnesium bromide with the formation of

1,4-diphenylbutene-2. The latter, when treated with bromine, gave 1,4-diphenyl-2,3-dibromobutene, which when heated with quinoline gave trans-trans-diphenylbutadiene-1,3 in 92% yield.

$$\underset{\text{(I)}}{C_6H_5{-}CH_2{-}CH{=}CH{-}CH_2Cl} + C_6H_5MgBr \longrightarrow \underset{\text{(II)}}{C_6H_5CH_2{-}CH{=}CH{-}CH_2C_6H_5} \xrightarrow{+Br_2}$$

$$\longrightarrow \underset{\text{(III)}}{C_6H_5{-}CH_2{-}CHBr{-}CHBr{-}CH_2{-}C_5H_5} \xrightarrow{\text{хинолин}} \underset{\text{(IV)}}{C_6H_5{-}CH{=}CH{-}CH{=}CH{-}C_6H_5}.$$

EXPERIMENTAL

4-Chloro-1-phenylbutene-2 (I). The reaction was carried out in a flask with stirrer, a thermometer and a dropping funnel. Beside the stirrer, two tubes were inserted in the wide neck – a divinyl inlet and a gas outlet; the latter was connected to a reflux condenser. In a typical example, 19 g of aniline was dissolved in 50 ml of concentrated acid and diazotized with a solution of 14 g of sodium nitrite in 20 ml of water; during the diazotization, about 50 g of ice was added; thus, the total volume was about 150 ml. 16 g of divinyl was dissolved in 200 ml of acetone, cooled to −5°, and was transfered to the reaction flask, which was well cooled and in which had previously been placed 8 g of $CuCl_2 \cdot 2H_2O$ in 15 ml of water and 7.5 g of calcium oxide. The cold (0°) solution of the diazo compound was added dropwise to the vigorously stirred mixture. At 6-7° a considerable evolution of nitrogen began, which was collected in a gasometer after previously being freed from acetone vapor and divinyl by passing through washing bottles with water, bromine solution, dioxane and again water. At the same time, divinyl was passed through the reaction mixture at a rate of 1 bubble per second. After 2 hours, the evolution of nitrogen ceased. The mixing was continued for a further $^1/_2$ hour and the temperature was allowed to rise to that of the room. 4 liters of nitrogen was isolated. 200 ml of ether was added to the layered liquid. The ether layer was separated, washed with water and dried with calcium chloride. After distilling off the ether, 28.1 g of a dark oil remained, which gave on distillation 1.6 g (7%) of chlorobenzene, 23.3 g (70%) of 4-chloro-1-phenylbutene-2 (I) and a residue of 3 g of tarry material.

The substance (I) was a slightly yellow oil.

B.p. 110-112° (6 mm), n_D^{20} 1.5402, d_4^{20} 1.0541, MR_D 49.50. $C_{10}H_{11}Cl\digamma_4$. Calc. 49.18.
Literature data: b.p. 107-112° (12 mm), n_4^{25} 1.5365, d_4^{20} 1.032 [14].
Found %: C 72.05; H 6.62; Cl 21.25. $C_{10}H_{11}Cl$. Calculated %: C 72.08; H 6.65; Cl 21.28.

The substance decolorized potassium permanganate solution and bromine water and mixed with the usual organic solvents.

The reaction between divinyl and phenyldiazonium chloride in the presence of magnesium oxide, sodium acetate, and free of aluminum oxide hydrate, copper oxide and zinc oxide was carried out in a similar way. The results of the experiments are given in the table.

2 g of (I) was oxidized in 50 ml of water, made alkaline with caustic potash, by the gradual addition of $KMnO_4$ with stirring. Benzoic acid was isolated from the filtrate after acidification.

Oxidation of 2 g of (I) with a solution of 11.2 g of $K_2Cr_2O_7$ and 6 ml of concentrated sulfuric acid in 50 ml of water also gave benzoic acid: m.p. 121°. A mixed m.p. was not depressed.

4-Bromo-1-phenylbutene-2. 150 ml of a solution of phenyldiazonium bromide was prepared by diazotizing at −4 to +2° 18.6 g of aniline in 83 ml of concentrated hydrobromic acid (d 1.385) with 14 g of sodium nitrite in 25 ml of water at −4 + 2°. The reaction with divinyl was carried out similarly to the experiment with phenyldiazonium chloride in the presence of lime, but instead of cupric oxide, 11.2 g of $CuBr_2$ was used and instead of calcium oxide, 4.8 g of magnesium oxide. The evolution of nitrogen proceeded at 3-7°. Distillation yielded 1.5 g (7.6%) of phenol, 17.5 g (56%) of bromobenzene, 14 g of 4-bromo-1-phenylbutene-2 and 2.5 g of a tarry material.

4-Bromo-1-phenylbutene-2 was a slightly yellow oil.
B.p. 118-121° (5 mm), n_D^{20} 1.5678, d_4^{20} 1.2660, MR_D 54.53. $C_{10}H_{11}Br\digamma_4$. Calc. 54.34.
Literature data [13]: b.p. 112-115° (14 mm). Found %: Br 37.80. $C_{10}H_{11}Br$. Calculated %: Br 37.86.

1,4-Diphenylbutene-2 (II). A solution of 16.7 g of 4-chloro-1-phenylbutene-2 (I) in 20 ml of absolute ether was added with stirring to a solution of phenylmagnesium bromide (from 15.7 g of bromobenzene and 2.4 g of magnesium in 40 ml of absolute ether). At the end of the reaction the mixture was heated to boiling for a further ½ hour, decomposed with 25 g of ice and acidified with dilute sulfuric acid. The ether layer was washed with water, alkali and again with water and dried with calcium chloride. The ether was distilled off and the residue was distilled in vacuum; we collected 14 g (63.7%) of a thick, slightly yellow oil.

B.p. 135-160° (8 mm) on cooling to −0° it crystallized; b.p. 45-45.5° (from methanol). Literature data: m.p. 45-46° [15]. Found %: C 92.31; H 7.32. $C_{16}H_{16}$. Calculated %: C 92.26; H 7.73.

1,4-Diphenyl-3,4-dibromobutane (III). 3 ml of bromine was carefully added with cooling and stirring to 10.4 g of 1,4-diphenylbutene-2 (II) in 50 ml of methanol. A heavy, transparent oil separated out and crystallized: m.p. 81° (from methanol). The yield was 18 g (98%).

Found %: Br 43.61. $C_{16}H_{16}Br_2$. Calculated %: Br 43.42.

Trans-trans-1,4-diphenylbutadiene-1,3 (IV). 7.4 g of 1,4-diphenyl-2,3-dibromobutane (III) was heated for ½ hour at 160° with 45 ml of quinoline; on cooling the dark liquid was poured into 100 ml of 20% sulfuric acid. The precipitate was extracted with ether, the extract was washed with water and dried with calcium chloride. After distilling off the ether we obtained 3.8 g (92%) of a substance with m.p. 150.5° (from glacial acetic acid).

Literature data: m.p. 147°, 152° [16].

Condensation of (IV) with maleic anhydride. 2 g of (III) was carefully heated with 1 g of maleic anhydride until it gently boiled. After cooling the melt, it was recrystallized from benzene: m.p. 206-207°.

Literature data: m.p. 207° [17].

4-Bromo-1-phenylbutene-2. 8.3 g of substance (I) and 9.5 g of finely powdered potassium bromide in 30 ml of acetone were heated in a sealed tube at 100° for 8 hours. The mixture was treated with water, the organic layer was extracted with ether and dried with calcium chloride. After distilling off the solvent, we obtained 9 g of oil, which yielded on distillation 2.5 g of unreacted (I) and 5 g of 4-bromo-1-phenylbutene-2. B.p. 116-118° (3 mm).

Found %: Br 37.68. $C_{10}H_{11}Br$. Calculated %: Br 37.68.

4-Iodo-1-phenylbutene-2. 7 g of substance (I) and 10 g of potassium iodide were boiled for 4 hours in 40 ml of alcohol. The liquid and the precipitate were treated with water. The oily layer was washed with sodium thiosulfate, extracted with ether and dried over calcium chloride. On evaporating off the ether we obtained 9 g of a heavy oil which decomposed on distilling in vacuum (4 mm).

n_D^{20} 1.5940, d_4^{20} 1.5100, MR_D 58.01. $C_{10}H_{11}I\overline{F}_4$. Calc. 57.11.

4-Thiocyano-1-phenylbutene-2. 8.3 g of substance (I) and 7.8 g of potassium thiocyanate were boiled for 6 hours in alcohol. The reaction mixture was worked up as in the previous experiment. We obtained 6.7 g (70.5%) of a slightly yellow oil with a characteristic smell.

B.p. 135-138° (5 mm), n_D^{20} 1.5748, d_4^{20} 1.0685. Found %: N 7.16. $C_{11}H_{11}NS$. Calculated %: N 7.40.

4-Diethylamino-1-phenylbutene-2. A mixture of 8.3 g of substance (I), 12.6 ml of diethylamine and 10 ml of water was heated for 2 hours in a sealed tube at 100°. The organic layer was dissolved in ether, washed with water to a negative reaction for ionic chlorine and dried with solid caustic potash. We obtained 10 g (98%) of a colorless oil, which was difficultly soluble in water.

B.p. 130° (9 mm), n_D^{20} 1.5158, d_4^{20} 0.9060, MR_D 67.71. $C_{14}H_{21}N\overline{F}_4$. Calc. 66.72. Found %: N 6.52. $C_{14}H_{21}N$. Calculated %: N 6.89.

4-Diethylamino-1-phenylbutene-2 hydrochloride. A stream of dry hydrogen chloride was passed through a solution of 2 g of 4-diethylamino-1-phenylbutene-2 in 20 ml of absolute ether. We obtained 2.25 g (95%) of colorless crystals of the amine hydrochloride: m.p. 85°.

Found %: Cl 14.58. $C_{14}H_{22}NCl$. Calculated %: Cl 14.79.

1-Phenylbutadiene-1,3 (V) and 4-ethoxy-1-phenylbutene-2 (VI). To a solution of sodium ethylate (from 2.3 g of sodium and 60 ml of anhydrous alcohol) cooled to 0°, 15.3 g of substance (I) was added with stirring, whereupon the temperature rose to 6° and the solution became quite cloudy. The mixture was heated to 50-60° for 2 hours, diluted with 60 ml of water and extracted with ether and the extract was washed with water and dried with magnesium sulfate. After distilling off the solvent, we obtained 16 g of oil, which gave two fractions on distillation in vacuum

1st fraction 5.5 g (43%) – 1-phenylbutadiene-1,3 (V):
b.p. 85-87° (10 mm), n_D^{20} 1.5903, d_4^{20} 0.9270, MR_D 47.41. $C_{10}H_{10}F_5$. Calc. 43.85.

A mixture of 1.5 g of the diene obtained with 1 g of maleic anhydride was heated on a water bath for 1.5 hours. The solidified melt was recrystallized from benzene: m.p. 120° (literature data: m.p. 119-120° [17]). According to the constants, the diene obtained under these conditions corresponded to cis-1-phenylbutadiene-1,3. Literature data: b.p. 86° (11 mm), n_D^{28} 1.5950 [18].

2nd fraction 6.5 g (37.5%) – a colorless oil corresponding to the ether 4-ethoxy-1-phenylbutene-2.

B.p. 117-118° (10 mm), n_D^{20} 1.5115, d_4^{20} 0.9446, MR_D 55.94. $C_{12}H_{16}OF_4$. Calc. 55.19.
Found %: C 81.96; H 9.36. $C_{12}H_{16}O$. Calculated %: C 81.77; H 9.15.

1-Phenyl-4-chloro-2,3-dibromobutane. 8.3 g of substance (I), dissolved in 30 ml of dioxane, was added in portions with stirring and cooling to 16.8 g of dioxane dibromide (from 8.8 g of dioxane and 2.7 g of bromine [19]). The reaction was complete in a few minutes. The dioxane was distilled off in vacuum (100 mm). The residue was a clear, colorless oil. The yield was 16.3 g (100%). In the cold it set to a viscous mass.

n_D^{20} 1.5927, d_4^{20} 1.6902 MR_D 65.64. $C_{10}H_{11}ClBr_2$. Calc. 65.44. Found %: C 53.28; H 4.71. $C_{10}H_{11}ClBr_2$. Calculated %: C 53.03; H 4.90.

SUMMARY

1. 4-Chloro-1-phenylbutene-2 was obtained in good yields (60-70%) by treating divinyl with phenyldiazonium chloride in a water-acetone solution in the presence of cupric chloride and calcium or magnesium oxides. A number of properties and reactions of the chlorophenylbutene obtained were studied.

2. A reaction mechanism was proposed for the halogenoarylation of divinyl by aromatic diazonium salts in the presence of cupric halides.

LITERATURE CITED

[1] K. Meyer, A. Irschik and H. Schlosser, Ber. 87, 1741 (1914).

[2] K. Meyer, Ber. 52, 1468 (1919).

[3] A. P. Terentyev and A. A. Demidova, J. Gen. Chem. 7, 2464 (1937).

[4] A. P. Terentyev, E. V. Vinogradova and G. D. Galperi, Sci. Rep., Moscow State Univ. 6, 243, 249 (1936); A. P. Terentyev, J. Gen. Chem. 7, 2026 (1937); A. P. Terentyev and E. M. Ivanova, J. Gen. Chem. 7, 2028 (1937); A. P. Terentyev 4, 535 (1937); A. P. Terentyev and A. A. Demidova, Bull. Acad. Sci. USSR, Div. Chem. Sci. 1941, 137.

[5] H. Meerwein, E. Buchner and K. Emster, J. prakt. Chem. 152, 237 (1939).

[6] J. Rai and K. Mathur, J. Ind. Chem. Soc. 24, 383 (1947); Ch. A., 42, 5881c (1948).

[7] H. H. Hodgson and S. Birthwell, J. Chem. Soc. 1942, 720; 1944, 18.

[8] W. Waters, Chemistry of Free Radicals (Moscow, 1948), 180.

[9] C. F. Coelsch and V. Boekelheide, J. Am. Chem. Soc. 66, 412 (1944).

[10] E. Muller, Ang. Chem. 61, 179 (1949).

[11] A. N. Nesmeyanov and L. G. Makarova, Bull. Acad. Sci. USSR, Div. Chem. Sci. 1947, 1213.

[12] O. A. Reutov, Proc. Acad. Sci. 87, 73 (1952).

[13] J. Braun and G. Lemke, Ber. 55, 3547 (1922).

[14] F. Semeniuk and G. L. Jenkins, J. Am. Pharm. Assoc. Sci. Ed. 37, 118 (1948); C. A. 42, 5410 (1948).

[15] F. Straus, Liebigs. Ann. 342, 254 (1905).

[16] R. Kuhn and A. Winterstein, Helv. Chim. Acta, 11, 87 (1928).

[17] O. Diels, K. Alder and P. Price, Ber. 62, 2081 (1929).

[18] J. E. Muskat and M. Herman, J. Am. Chem. Soc. 53, 252 (1931).

[19] L. A. Yanovskaya, A. P. Terentyev and L. I. Belenky, J. Gen. Chem. 22, 1594 (1952).(T.p. 1635).*

Received May 30, 1955

Moscow State University

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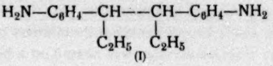
* T.p = C. B. Translation pagination.

SYNTHESIS OF SOME DERIVATIVES OF p, p'-DIAMINO-MESO-3, 4-DIPHENYLHEXANE

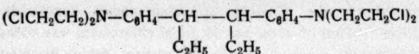
S. F. Torf and N. V. Khromov-Borisov

After it was found that β, β'-bis-dichlorodiethylamines had a certain retarding effect on the growth of malignant tumors, various investigators synthesized and tested different amino compounds containing β-chloroethyl radicals. The introduction of chloroethyl radicals into p, p'-diamino-meso-3, 4-diphenylhexane (I) which is similiar in structure to synestrol is described in this paper. Besides the di-p,p'-(bis-β-chloroethylamino)-meso-3, 4-diphenylhexane (II) obtained by this method, the following, which are similiar to it in structure, were also tested: di-p, p'-(bis-β-hydroxyethylamino)-meso-3, 4-diphenylhexane (III), bis-p, p'-(diethylamino)-meso-3, 4-diphenylhexane (IV) and the original p, p'-diamino-meso-3, 4-diphenylhexane (I).



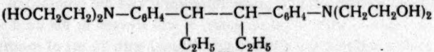
$$H_2N-C_6H_4-\underset{C_2H_5}{\underset{|}{CH}}-\underset{C_2H_5}{\underset{|}{CH}}-C_6H_4-NH_2$$

(I)



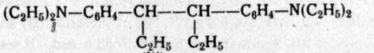
$$(ClCH_2CH_2)_2N-C_6H_4-\underset{C_2H_5}{\underset{|}{CH}}-\underset{C_2H_5}{\underset{|}{CH}}-C_6H_4-N(CH_2CH_2Cl)_2$$

(II)



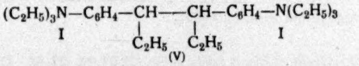
$$(HOCH_2CH_2)_2N-C_6H_4-\underset{C_2H_5}{\underset{|}{CH}}-\underset{C_2H_5}{\underset{|}{CH}}-C_6H_4-N(CH_2CH_2OH)_2$$

(III)



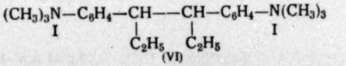
$$(C_2H_5)_2N-C_6H_4-\underset{C_2H_5}{\underset{|}{CH}}-\underset{C_2H_5}{\underset{|}{CH}}-C_6H_4-N(C_2H_5)_2$$

(IV)



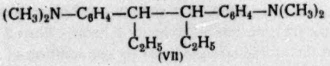
$$\underset{I}{(C_2H_5)_3N}-C_6H_4-\underset{C_2H_5}{\underset{|}{CH}}-\underset{C_2H_5}{\underset{|}{CH}}-C_6H_4-\underset{I}{N(C_2H_5)_3}$$

(V)



$$\underset{I}{(CH_3)_3N}-C_6H_4-\underset{C_2H_5}{\underset{|}{CH}}-\underset{C_2H_5}{\underset{|}{CH}}-C_6H_4-\underset{I}{N(CH_3)_3}$$

(VI)



$$(CH_3)_2N-C_6H_4-\underset{C_2H_5}{\underset{|}{CH}}-\underset{C_2H_5}{\underset{|}{CH}}-C_6H_4-N(CH_3)_2$$

(VII)

The synthesis of the compounds mentioned was carried out in the following way. p, p'-Diamino-meso-3, 4-diphenylhexane [1, 2] (I) was treated with ethylene chlorohydrin in the presence of calcium carbonate and sodium iodide (which accelerated the reaction somewhat and improved the yield) to give di-p, p'-(bis-β-hydroxyethylamino)-meso-3, 4-diphenylhexane (III) which was then converted by phosphorus oxychloride into di-p, p'-(bis-β-chloroethylamino)-meso-3, 4-diphenylhexane (II) under the conditions described by Ross [3] for the synthesis of β-chloroethylamino derivatives of the aromatic series. p, p'-Bis-(diethylamino)-meso-3, 4-diphenylhexane (IV) was obtained by the method described by us earlier [4]. It could also be obtained from p, p'-bis-(diethylamino)-

meso-3,4-diphenylhexane (V) [4] by the reaction of the latter with sodium ethylate. p,p'-Bis-(dimethylamino)-meso-3,4-diphenylhexane (VII) was obtained by the same method, from p,p'-bis-(dimethylamino)-meso-3,4-diphenylhexane diiodomethylate (VI) [4].

The materials (I-IV) were tested by N. A. Vodolazskaya in the Experimental Chemical Therapy Laboratory of the Institute of Experimental Cancer Pathology and Therapy of the USSR Academy of Medicine. The tests showed that when the materials were introduced in the form of a suspension in glycerin, diluted with water, in doses of 100-1000 mg/ kg into the stomach of mice with grafted Erlich tumors, no retarding effect was observed on the tumor growth.

EXPERIMENTAL

Di-p,p'-(bis-β-hydroxyethylamino)-meso-3,4-diphenylhexane (III). A mixture of 8 g of p,p'-diamino-meso-3,4-diphenylhexane (I), 10.5 g of calcium carbonate, 11 g of sodium iodide, 220 ml of ethyl alcohol, 120 ml of water and 44 ml of ethylene chlorohydrin was refluxed on a water bath for 70 hours (with interruptions). For the last 25-30 hours it boiled better with mechanical stirring as the reaction mixture began to bump up into the condenser vigorously. After cooling, the precipitate was filtered off (13.5 g), boiled with 50 ml of alcohol and, after cooling, again filtered off (12.9 g). Then it was boiled with 300 ml of alcohol in the presence of activated charcoal and the undissolved precipitate was filtered off hot. On cooling the filtrate yielded 1.8 g of a white precipitate with m.p. 207-209°. The undissolved precipitate was again treated with the mother liquors in the same way 4 times. This yielded a further 6.85 g of material with m.p. 207-209°. In all we obtained 8.65 g (65.3%) of the white substance (III).

Found %: C 70.30, 70.38; H 9.11, 9.09; N 6.23, 6.33. $C_{26}H_{40}O_4N_2$. Calculated %: C 70.27; H 9.01; N 6.31.

Di-p,p'-(bis-β-chloroethylamino)-meso-3,4-diphenylhexane (II). 6 g of di-p,p'-(bis-β-hydroxyethylamino)-meso-3,4-diphenylhexane was added over a period of 20 minutes to 15 ml of phosphorus oxychloride, cooled in ice water, and after this, the reaction mixture was heated on a boiling water bath for 1 hour with a reflux condenser and a calcium chloride tube. Then the excess phosphorus oxychloride (7 ml) was distilled in vacuum on a boiling water bath. 100 ml of water and 50 ml of chloroform was added to the cooled residue and the mixture was periodically carefully shaken by hand. The viscous residue disolved only after 2.5 hours. The aqueous layer was separated and washed with 10 ml of chloroform and the chloroform solutions were combined. After washing the chloroform solution with 10 ml of water, it was treated in the cold with active charcoal. On the following day the chloroform solution was filtered and diluted with 70 ml of methyl alcohol. After 20 minutes precipitation began. After cooling in ice for 3 hours, the precipitate was filtered off and washed with a mixture of chloroform and methyl alcohol. We obtained 5.4 g (77.1%) of material (II) with m.p. 149-151°, which was white with a grey tint. On storage in air, the material turned slightly red. It was insoluble in dilute hydrochloric acid. On boiling a solution in anhydrous alcohol with an alcohol solution of $AgNO_3$ for 30-40 minutes, the chlorine was completely precipitated (in the form of AgCl).

Found %: C 60.11, 60.20; H 7.03, 7.05; N 5.45, 5.50; Cl 27.33, 27.68. $C_{26}H_{36}N_2Cl_4$. Calculated %: C 60.23; H 6.95; N 5.41; Cl 27.41.

p,p'-Bis-(diethylamino)-meso-3,4-diphenylhexane (IV). 0.18 g of p,p'-bis-(diethylamino)-meso-3,4-diphenylhexane diiodoethylate was added to a solution of sodium alcoholate prepared from 0.05 g of sodium and 15 ml of anhydrous alcohol, and the mixture was refluxed for 2 hours. Then 2 ml of water was added to the solution, the mixture was heated until the precipitate produced by the addition of the water had dissolved and the solution was filtered while hot. After cooling, the precipitate was filtered off. We obtained 0.06 g (60.7%) of the white substance (IV) with m.p. 158-160°.

Found %: N 7.39, 7.37. $C_{26}H_{40}N_2$. Calculated %: N 7.37.

A mixed m.p. with a sample of p,p'-bis-(diethylamino)-meso-3,4-diphenylhexane, obtained by another method [4], was not depressed.

p,p'-Bis-(dimethylamino)-meso-3,4-diphenylhexane (VII). 0.3 g of p,p'-bis-(dimethylamino)-meso-3,4-diphenylhexane diiodomethylate was added to a solution of sodium alcoholate, obtained from 0.3 g of sodium and

15 ml of anhydrous alcohol, and the mixture was refluxed for 2.5 hours. Then 30 ml of water was added to the hot solution, the precipitate was filtered off from the warm solution, washed with warm water and dried at 60° The weight was 0.15 g (62.5%) and the m.p. 202-204°. After recrystallization from 30 ml of alcohol, we obtained 0.1 g of a white substance (VII) with m.p. 210-212°.

Found %: C 81.48, 81.62; H 9.98, 9.82; N 8.60, 8.71. $C_{22}H_{32}N_2$. Calculated %: C 81.48; H 9.88; N 8.64.

SUMMARY

1. Di-p,p'-(bis-β-hydroxyethylamino)-meso-3,4-diphenylhexane and di-p,p'-(bis-β-chloroethylamino)-meso-3,4-diphenylhexane were synthesized from p,p'-diamino-meso-3,4-diphenylhexane. p,p'-Bis-(dimethylamino)-meso-3,4-diphenylhexane and p,p'-bis-(diethylamino)-meso-3,4-diphenylhexane were obtained from the iodide salts of the corresponding quaternary base.

2. When p,p'-diamino-meso-3,4-diphenylhexane, p,p'-bis-(diethylamino)-meso-3,4-diphenylhexane, di-p,p'-(bis-β-hydroxyethylamino)-meso-3,4-diphenylhexane and di-p,p'-(bis-β-chloroethylamino)-meso-3,4-diphenylhexane were tested on mice with grafted Erlich tumors no retarding effect on the tumor growth was observed when these materials were introduced in doses of 100-1000 mg/kg in the form of a suspension in glycerin, diluted with water.

LITERATURE CITED

[1] G. Fodor and I. Wein, J. Chem. Soc. 1948, 685, 686.

[2] S. F. Torf and N. V. Khromov-Borisov, J. Gen. Chem. 24, 1681 (1954) (T. p. 1653).*

[3] W. C. I. Ross, J. Chem. Soc. 1949, 190.

[4] S. F. Torf and N. V. Khromov-Borisov, J. Gen. Chem. 24, 2170, 2171 (1954) (T.p. 2137).*

Received October 25, 1955

Institute of Experimental Medicine of
the Academy of Medicine USSR

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* T. p. = C. B. Translation pagination.

ATTEMPTED SYNTHESIS OF 7-AMINOHEPTANOIC ACID BY THE PARTIAL HYDROLYSIS OF PIMELODINITRILE WITH HYDROGEN PEROXIDE

M. N. Bogdanov

7-Aminoheptanoic acid is the monomer for obtaining a fibre-forming and technically important polyamide resin [1] which contains almost no fractions with low molecular weight. Due to this the investigation of methods of synthesizing it is of considerable interest. Pimelodinitrile, which is quite readily obtainable from furfurol [2], is one of the possible raw materials for 7-aminoheptanoic acid. 7-Aminoheptanoic acid may be synthesized from pimelodinitrile in two ways: a) by partial hydrogenation of the dinitrile with the formation of 7-aminoheptanonitrile and hydrolysis of the latter into the free aminoacid· b) by partial saponification of the dinitrile into 7-aminoheptanoamide and subsequent hydrolysis of the amide. The first scheme for synthesizing 7-aminoheptanoic acid has already been approved [1]; the second has not been described in the literature and is the subject of this investigation.

$$CN(CH_2)_5CN \longrightarrow CN(CH_2)_5CONH_2 \longrightarrow NH_2CH_2(CH_2)_5CONH_2.$$

Alkaline hydrogen peroxide – a reagent that had already been used earlier for the partial hydrolysis of the dinitriles of adipic and sebacic acids [3] – was used for converting pimelodinitrile into 5-cyanocaproamide. After a number of experiments a method was worked out by which 5-cyanocaproamide was obtained in 68% yield allowing for the unreacted dinitrile. Besides the monoamide, about 19% of pimelodiamide was also formed. The reaction was carried out by mixing 1 volume of dinitrile with 4 volumes of a 3% aqueous solution of H_2O_2, made alkaline with KOH, at 2-4° and heating them for a short time. The reaction products were easily separated by extraction of the residue from evaporation to dryness of the aqueous part of the reaction emulsion. The unreacted dinitrile, with no preliminary purification, was again used for the following hydrolysis operation. An increase in temperature and the use of solvents sharply decreased the amount of dinitrile reacting; an increase in the amount and concentration of H_2O_2 increased the amount of reacted dinitrile, but simultaneously increased the relative yield of pimelodiamide.

The second stage of the scheme – the reduction of 5-cyanocaproamide into aminoheptanoamide – met with difficulties.

Hydrogenation with molecular hydrogen under pressure in the presence of Raney nickel catalyst was accompanied by ammonia separation and resulted in the formation, not of a primary, but of a secondary amine, di-(6-carboxyhexyl)-amine, as the main reaction product:

$$2CN(CH_2)_5CONH_2 \xrightarrow{4H_2} NH_2CO(CH_2)_6NH(CH_2)_6CONH_2 + NH_3.$$

The 5-cyanocaproamide and di-(6-amidohexyl)-amine synthesized and the di-(6-carboxyhexyl)-amine, obtained by hydrolysis of the latter, are new compounds.

EXPERIMENTAL

Partial hydrolysis of pimelodinitrile (typical experiment). A mixture of 103 ml of 3% H_2O_2 and 2 ml of 45% KOH was placed in a flask submerged in an ice bath and fitted with an efficient stirrer. 25 ml of pimelodinitrile was added with mixing over a period of 50 minutes to the hydrogen peroxide, which was cooled to 2-4°. Then, without stopping the stirrer, the flask was heated on a boiling water bath for 10-15 minutes. The suspension formed was cooled to room temperature, transfered to a separating funnel and the unreacted dinitrile was separated off from the aqueous solution. This residual dinitrile was made up to 25 ml with fresh dinitrile and was used in a new hydrolysis. In all, three subsequent operations were carried out using the unreacted pimelodinitrile. The combined aqueous solutions were neutralized and concentrated to 100 ml. On cooling the solution, a further small amount of unreacted dinitrile separated. After separating off the dinitrile, the solution was evaporated to dryness and the residue was mixed with 50 ml of benzene.

The material isolated was separated off, and extracted with 70 ml of boiling dichloroethane and the insoluble part "A" was filtered off. On cooling the dichloroethane solution, 15 g of a colorless substance with m.p. 86-88° separated. After crystallization from a mixture of dichloroethane and benzene, it melted at 90-91°. The amide of cyanocaproic acid obtained was readily soluble in water and alcohols, slightly less in acetone and difficultly soluble in benzene and ether and crystallized from dichloroethane (small plates), benzene and a concentrated solution of acetone; on heating with alkali, ammonia was strongly evolved.

Found %: C 59.23, 59.39; H 8.57, 8.59. $C_7H_{12}ON_2$. Calculated %: C 60.00; H 8.57.

Substance "A" was extracted with 50 ml of boiling ethanol, the solution filtered free from the mineral part and was evaporated to dryness. The residue was 4.5 g of a substance with m.p. 150-156° and after crystallization from ethanol, it melted at 169-170°.* On heating with alkali, ammonia was strongly evolved.

Found %: C 54.07, 52.96; H 8.97, 9.22. $C_7H_{14}O_2N_2$. Calculated %: C 53.17; H 8.86.

From 44 ml of pimelodinitrile, used for the three subsequent experiments, 20 ml reacted and 25 ml was recovered as a yellow, turbid oil, which contained a small amount of water. The yield of the amide of 5-cyanocaproic acid, allowing for the dinitrile recovered, was about 68%, the pimelic diamide – 19%.

Hydrogenation of 5-cyanocaproamide. 14.5 g of amide in 100 ml of dioxane with 7 g of Raney nickel catayst was hydrogenated in a horizontal rotating autoclave for 2 hours at 95-105°. The initial hydrogen pressure in the autoclave was 90 atm., the final (after hydrogenation), 86 atm. When the pressure was let down there was a strong odor of ammonia. The reaction product – a crystalline, colorless material – was dissolved in hot methanol, after decantation of the dioxane. The solution was filtered free from catalyst and evaporated to dryness. The residue crystallized from 40 ml of butanol, the crystals were washed with 5 ml of butanol and 20 ml of acetone and twice recrystallized from water. We obtained 6.4 g of di-(6-amidohexyl)-amine with m.p. 150.5-151.5°. The material was difficultly soluble in hot ether and benzene; it crystallized readily from butanol and water and not quite so well, due to the greater solubility, from methanol and ethanol.

Found: M 268, 268. $C_{14}H_{29}O_2N_3$. Calculated: M 271.

Hydrolysis of di-(6-amidohexyl)-amine. A mixture of 1.5 g of di-(6-amidohexyl)-amine, 15 ml of water and 10 g of $Ba(OH)_2 \cdot 8H_2O$ was boiled for 13 hours, then diluted with 100 ml of water, filtered and saturated with CO_2.

The $BaCO_3$ precipitate was separated off and to the filtrate was added dilute sulfuric acid until the last drop of acid produced no precipitate. The material was filtered off, dissolved in 30 ml of water by adding alkali, and isolated from the solution by neutralization to litmus with dilute H_2SO_4. We obtained 0.89 g of di-(6-carboxyhexyl)-amine with m.p. 212.5-213.5°, which was insoluble in acetone, ether, benzene and ethyl acetate, moderately soluble in hot water and methanol and crystallized from boiling water. The material had amphoteric properties and readily dissolved on treating its suspension in water with acid or alkali.

Found %: C 61.81; 61.84; H 9.44, 9.54, M** 261, 268. $C_{14}H_{27}O_4N$. Calculated %: C 61.48; H 9.95. M 273.

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* For diamide of pimelic acid m.p. 170-173° [4].

** By titrating a solution of the material in excess alkali with sulfuric acid in the presence of phenolphthalein (neutralization point – transition into the monosodium salt).

SUMMARY

1. A method for the partial hydrolysis of pimelodinitrile with alkali hydrogen peroxide in a yield of up to 68% of 5-cyanocaproamide, was worked out to obtain 7-aminoheptanoic acid from pimelodinitrile.

2. The hydrogenation of 5-cyanocaproamide into 7-aminoheptanoamide with molecular hydrogen in the presence of Raney nickel catalyst resulted in the formation not of 7-aminoheptanoamide, but of di-(6-amidohexyl)-amine as the main reaction product.

3. New compounds were synthesized: 5-cyanocaproamide, di-(6-amidohexyl)-amine and di-(6-carboxyhexyl)-amine.

LITERATURE CITED

[1] W. Munch and Melland, Textilberichte 32, 823 (1951).

[2] O. Cass, Ind. Eng. Chem. 40, 219 (1948).

[3] R. Wiley and H. Morgan, J. Org. Chem. 15, 800 (1950).

[4] G. Ernst and G. Hofman, C. A. 46, 7049a (1952).

Received November 9, 1955

The All-Union Institute for the Scientific
Investigation of Synthetic Fibers

INVESTIGATIONS IN THE FIELD OF ACETYLENIC AMINES

III. ISOMERIZATION OF DIALKYLAMINOACETYLENES

A. T. Babayan and N. G. Vartanyan

It was shown in a previous report [1] that the presence of a dimethylamino group in the α-position to the acetylenic carbon atom facilitates isomerization (according to Favorsky) of 1-dimethylaminobutyne-2 into 1-dimethylaminobutyne-3 by the action of metallic sodium. A series of dialkylaminoacetylenes were synthesized by us and treated with metallic sodium in an ether medium to find out the effect that the nature of the radicals, as well as the position of the dialkylamino group, had on the isomerization rate.

The experimental results are summarized in the table.

An increase in radicals connected to nitrogen, as well as separation of the amino-group from the acetylene carbon atom, leads to a decrease in isomerization rate. Using 1-dimethylamino and 1-diethylaminobutynes-2 as examples, it was shown that the reaction proceeded considerably faster in boiling ether. Besides the isomerization product, a lower boiling fraction, 1-dialkylaminobutene-2, was also obtained, i.e. the hydrogenation product of the original 1-dialkylaminobutyne-2. We tried isomerization with sodamide to eliminate hydrogenation [2]. However, we were unable to bring about isomerization with sodamide either in ether or in xylene, even by heating on a boiling water bath for many hours – the product was completely recovered unchanged. Apparently, the presence of the dialkylamino-group did not have any noticeable effect in this case on the isomerization reaction.

As is known, the reverse reaction under the action of alcoholic caustic potash, which results in doubly substituted acetylenic hydrocarbons, proceeds at a relatively higher temperature. Thus, for example, the conversion of ethylacetylene [3] into dimethylacetylene is carried out at 170° and higher. In exactly the same way, propylacetylene may be isomerized into methylethylacetylene only by heating for 24 hours at 170°. Experiments showed that this reaction also proceeded more readily in the presence of the dialkylamino group; 1-dimethylaminobutyne-3 was almost completely isomerized into 1-dimethylaminobutyne-2 by heating for 3 hours on a boiling water bath.

Data taken from the literature [3, 4] on the conditions of isomerization of the corresponding hydrocarbons are also given in the table for comparison.

The starting amines with three different radicals were obtained by the method we described earlier [5], while the others were obtained by the dehydrochlorination of 1-dialkylamino-3-chlorobutenes-2 [6], obtained, in their turn, by reaction of the dialkylamine with 1,3-dichlorobutene-2. 1-Dimethylaminopentynes-3 were obtained by the reaction of the sodium derivative of 1-dimethylaminobutyne-3 with methyl iodide [7].

The information in these reports serves as a basis for our proposal of a way of synthesizing various dialkylaminoacetylenes by the scheme:

$$R_2NH + CH_3CCl{=}CH{-}CH_2Cl \longrightarrow R_2N{-}CH_2CH{=}CCl{-}CH_3 \xrightarrow{NaOH}$$

$$R_2N{-}CH_2C{\equiv}C{-}CH_3 \xrightarrow{Na} R_2N{-}CH_2CH_2C{\equiv}CNa \xrightarrow{R'I}$$

$$R_2N{-}CH_2CH_2C{\equiv}C{-}R' \xrightarrow{Na} \text{etc.}$$

Due to the accessibility of 1,3-dichlorobutene-2 and the relative facility of 1-dialkylaminobutyne-2 isomerization it seems to us that this method deserves attention.

EXPERIMENTAL

1-Dibenzylamino-3-chlorobutene-2. A mixture of 197 g of dibenzylamine, 62.5 g of 1,3-dichlorobutene-2 and 55 ml of alcohol was heated for 10 hours on a boiling water bath. Then ether was added to the mixture, the precipitate was filtered off and the ether solution was washed with water, dried and distilled. We obtained 126.4 g (88.5%) of 1-dibenzylamino-3-chlorobutene-2.

B.p. 196.5° at 7 mm, d_4^{20} 1.0670, n_D^{20} 1.5636, MR_D 86.957; calc. 86.462. Found %: N 5.11. $C_{18}H_{20}NCl$. Calculated %: N 4.9.

Melting point of the picrate (from alcohol) 145-146°.

1-Dibenzylaminobutyne-2 (I). A mixture of 62.2 g of 1-dibenzylamino-3-chlorobutene-2, 22 g of potassium hydroxide and 60 ml of polyethylene glycol was heated for 4.5 hours with stirring. The upper layer was separated, washed with water, dried and distilled. We obtained 45.7 g (79.2%) of 1-dibenzylaminobutyne-2 (I).

Found %: N 5.84. $C_{18}H_{13}N$. Calculated %: N 5.62.

Melting point of the picrate (from alcohol) 154-155°.

Isomerization of 1-(methylethylamino)-butyne-2 (II). 2.3 g of sodium was put into 70 ml of absolute ether. 16 5 g of (II) was added with continuous stirring. Stirring was continued for 12 hours. The acetylide formed was filtered off through a layer of dry sand, washed with ether and decomposed with ether in an ether medium. The ether layer was dried and distilled. We obtained 4.7 g (28%) of 1-(methylethylamino)-butyne-3 (III).

Found %: N 12.88. $C_7H_{13}N$. Calculated %: N 12.613.

After distilling off the solvent, we obtained 11 g of a substance from the filtrate, which boiled in the range 120-136° and was a mixture of starting material and products of its isomerization and hydrogenation. 0.8 g of sodium was recovered.

Isomerization of 1-diethylaminobutyne-2 (IV). 2.3 g of sodium and 18.8 g of (IV) were added to 70 ml of ether. Mixing was continued for 20 hours. By working up as in the previous experiments, we obtained 6.8 g (36%) of 1-diethylaminobutyne-3 (V).

From the filtrate we obtained 9.5 g of a substance boiling in the range 140-150° (a mixture of starting material and products of isomerization and hydrogenation). 0.85 g of unreacted sodium was recovered.

Isomerization of 1-(methylbenzylamino)-butyne-2 (VI). 1.6 g of sodium and 18.5 g of (VI) was added to 70 ml of ether. Stirring was continued for 12 hours. We obtained 4.7 g of 1-(methylbenzylamino)-butyne-3 (VII).

Found %: N 8.21. $C_{12}H_{15}N$. Calculated %: N 8.09

From the filtrate we obtained 13 g of a substance boiling at 105-109° (7-8 mm). 0.9 g of sodium was recovered.

Isomerization of 1-dibenzylaminobutyne-2 (I). 1.15 g of sodium and 18.7 g of (I) were added to 70 ml of ether. Stirring was continued for 60 hours. The changes in the reaction mixture occurred very slowly. We obtained 4.8 g (27%) of 1-dibenzylaminobutyne-3 (VIII).

Found %: N 5.77. $C_8H_{19}N$. Calculated %: N 5.62.

From the filtrate we obtained 13 g of material boiling at 165-186° (7.5 mm).

Original compound	Boiling point (mm)	d_4^{20}	n_D^{20}	Reaction temperature	Time of reaction (in hours)
$CH_3C\equiv C-CH_3$ [4]	27—28°	—	—	100°	—
$(CH_3)_2N-CH_2C\equiv C-CH_3$ (XI)	112—115 (680)	0.7960	1.4383	Room 30—35	3 1
$\begin{matrix}CH_3\\C_2H_5\end{matrix}\!>\!N-CH_2C\equiv C-CH_3$ (II)	133—135 (680)	0.8165	1.4397	Room	12
$C_2H_5)_2N-CH_2C\equiv C-CH_3$ (IV)	148—150 (680)	0.8167	1.4440	Room 30—35	20 4
$\begin{matrix}CH_3\\C_6H_5CH_2\end{matrix}\!>\!N-CH_2C\equiv C-CH_3$ (VI)	115—116 (7.5)	0.9511	1.5210	Room	12
$(C_6H_5CH_2)_2N-CH_2C\equiv C-CH_3$ (I)	198 (12)	1.0086	1.5640	Room	60
$CH_3CH_2C\equiv C-CH_3$ [4]	55—56	—	—	100	4—5
$(CH_3)_2N-CH_2CH_2C\equiv C-CH_3$ (IX)	135—139 (680)	—	1.4450	Room	6
$CH_3CH_2C\equiv CH$ [3]	18.5	—	—	170	16
$CH_3CH_2CH_2C\equiv CH$ [3]	48—50	—	—	170	24
$(CH_3)_2N-CH_2CH_2C\equiv CH$ (XII)	102—105 (680)	0.78067	1.4275	95	3
$CH_3CH_2C\equiv CH$	18.5°	—	—	—	—
$(CH_3)_2N-CH_2CH_2C\equiv CH$ (XII)	102—105 (680)	0.7806	1.4275	53 50	116—117° 116—117
$\begin{matrix}CH_3\\C_2H_5\end{matrix}\!>\!N-CH_2CH_2C\equiv CH$ (III)	123—126 (680)	0.79327	1.4336	28	106—108
$(C_2H_5)_2N-CH_2CH_2C\equiv CH$ (V)	139—142 * (680)	0.7987 —	1.4361 —	36 44	107—108.5 —
$\begin{matrix}CH_3\\C_6H_5CH_2\end{matrix}\!>\!N-CH_2CH_2C\equiv CH$ (VII)	127 (16)	0.9372	1.5202	25.9	160—162 (iodomethylate)
$(C_6H_5CH_2)_2N-CH_2CH_2C\equiv CH$ (VIII)	176—178 (7.5)	1.0029	1.5612	27	146—148
$CH_3CH_2CH_2C\equiv CH$	48—50	—	—	—	—
$(CH_3)_2N-CH_2CH_2CH_2C\equiv CH$ (X)	120—123 ** (680)	0.7856	1.4299	51.7	100—101
$CH_3C\equiv C-CH_3$	27—28	—	—	—	—
$CH_3CH_2-C\equiv C-CH_3$	55—56	—	—	—	—
$(CH_3)_2N-CH_2C\equiv C-CH_3$ (XI)	112—115 (680)	0.7960	1.4383	84	118—119

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* According to literature data [8]: boiling point of 1-diethylaminobutyne – 385° at 110 mm, n_D^{18} 1.4390.

** According to literature data: 1-dimethylaminopentyne-4 has b.p. 129°, d_4^{20} 0.7985, n_D^{20} 1.4319 [9]; b.p. 72-73.5°, n_D^{15} 1.4340 [10.

Isomerization of 1-dimethylaminopentyne-3 (IX). 2.3 g of sodium and 15 g of (IX) were added to 70 ml of ether. Stirring was continued for 6 hours. We obtained 7.64 g (51.7%) of 1-dimethylaminopentyne (X).

From the filtrate we obtained 4.6 g of material boiling at 118-140° (680 mm).

Isomerization of 1-dimethylaminobutyne-2 (XI) in boiling ether. 4.6 g of sodium and 29.1 g of (XI) were added to 100 ml of absolute ether. It was heated on a water bath. Even after the first 25 minutes the clear mixture became black and then quickly became white. It was stirred for 70 minutes in all. We obtained 13.5 g (50%) of 1-dimethylaminobutyne-3 (XII). From the filtrate we obtained 14 g of a material boiling at 90-111°.

Isomerization of 1-diethylaminobutyne-2 (IV) in boiling ether. 1.4 g of sodium and 11.4 g of (IV) were added to 70 ml of ether. The reaction was carried out by heating on a boiling water bath. The reaction took 4 hours. We obtained 5.05 g (44%) of 1-diethylaminobutyne-3 (V).

Isomerization of 1-dimethylaminobutyne-3 (XII) with alcoholic alkali. A mixture of 8.6 g of 1-dimethylaminobutyne-3, 15 g of potassium hydroxide and 25 ml of 95% alcohol was heated on a boiling water bath for 3 hours. 7.8 g of amine was extracted from the reaction mixture. Two fractions were obtained by distillation: 1st fraction, b. p. 107-111°, 1.43 g; 2nd fraction, b. p. 111-117°, 5.8 g. Neither the first nor the second fraction gave a precipitate with a aqueous solution of silver nitrate, but on standing they formed a silver mirror as was the case with 1-dimethylaminobutyne-2 (XI). Mixed melting points of their picrates with the picrate of 1-dimethylaminobutyne-2 were not depressed.

SUMMARY

1. It was established that the rate of dialkylaminoacetylene isomerization by the action of metallic sodium depended both on the nature of the radicals introduced into the dialkylamino group and on the position of the latter in relation to the acetylenic carbon atom. Both radical increase and removal of the dialkylamino group resulted in a decrease in isomerization rate.

2. The presence of the dialkylamino group facilitated the isomerization of dialkylaminoalkylacetylene into doubly substituted acetylene by treatment with alcoholic alkali.

3. A comparatively simple method was proposed for the synthesis of dialkylaminoacetylenes with triple bonds in various positions in the molecule.

4. The following compounds are described for the first time: 1-dibenzylamino-3-chlorobutene-2, 1-dibenzylaminobutyne-2 (I), 1-(methylethylamino)-butyne-3 (III), 1-(methylbenzylamino)-butyne-3 (VII) and 1-dibenzylaminobutyne-3 (VIII).

LITERATURE CITED

[1] A. T. Babayan, G. M. Mkryan, and N. G. Vartanyan, Proc. Acad. Sci. Armenian SSR 19, 83 (1954).

[2] M. Bourguel, Compt. rend. 178, 1984 (1924); 179, 686 (1924).

[3] A. E. Favorsky, J. Russ. Chem. Soc. 19, 414 (1887).

[4] A. E. Favorsky, J. Russ. Chem. Soc. 19, 553 (1887).

[5] A. T. Babayan, N. G. Vartanyan, and I. Ya. Zurabov, J. Gen. Chem. 25, 1610 (1955).

[6] A. T. Babayan and A. G. Terzyan, Proc. Acad. Sci. Armenian SSR 9, 105 (1948); A. T. Babayan and N. G. Vartanyan, Bull. Acad. Sci. Armenian SSR, Phys.-Math. Nat. and Tech. Sci. 5, 39 (1952).

[7] I. Marszak and R. Epsztein, Bull. Soc. Chim. France, 1952, 441.

[8] R. Epsztein, M. Olomucki, and I. Marszak, Bull. Soc. Chim. 1953, 952.

[9] K. N. Campbell, F. C. Fatora, and B. K. Campbell, J. Org. Chem. 17, 1141 (1952).

[10] I. Marszak, R. Epsztein, and M. Olomucki, Compt. rend. 235, 1409 (1952).

Received November 14, 1955

Zoo-Veterinary Institute of Erivan

SYNTHETIC INVESTIGATIONS IN THE FIELD OF POLYENE COMPOUNDS

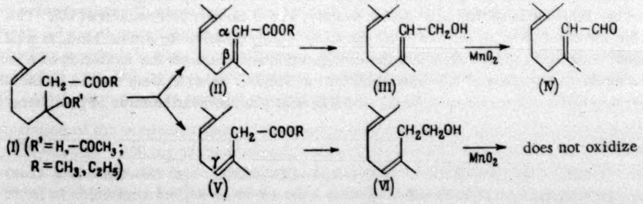
X. THE DIRECTION AND THE STEREOCHEMICAL SPECIFICITY OF THE DEHYDRATION OF ESTERS OF 3,7-DIMETHYLOCTEN-6-OL-3-IC-(1) ACID (β-HYDROXY-α, β-DIHYDROGERANIC) AND 5,9-DIMETHYLDECADIEN-2,8-OL-5-IC-(1) ACID

G. I. Samokhvalov, M. A. Miropolskaya, and N. A. Preobrazhensky

The dehydration of β-hydroxycarboxylic esters, obtained from the condensation of carbonyl compounds with halogenoacid esters by the Reformatsky reaction, was first studied on the condensation products of cyclic ketones. Structural factors and the dehydrating agent had an effect on the position of the double bond (cyclic or semicyclic) that was formed [1]. The effect of the dehydrating agent was also observed in the aliphatic series and due to it, mainly α, β- or β, γ- unsaturated isomers were obtained [2].

The content of the ester of 3,7-dimethyloctadien-2,6-ic-(1) acid (geranic) (II, R=H), which is usually obtained by oxidation of geranial, in the mixture of acids, formed by the dehydration of esters of β-hydroxy-α,β-dihydrogeranic acid (I, R'=H) varies greatly depending on the dehydration agent [3, 4].

We used pyrolysis of the acetyl derivative (I, R'=$COCH_3$), as well as the action of phosphorus tribromide and phosphorus oxychloride in pyridine for the dehydration of esters of β-hydroxy-α,β-dihydrogeranic acid in the synthesis of nerol and geraniol described by us [5]. The position of the double bond in the molecule of the dehydrated esters was proved by reducing them with lithium aluminum hydride. The α, β-unsaturated alcohols thus obtained were capable of being oxidized by activated manganese dioxide to the corresponding aldehydes. The isomeric β, γ-unsaturated alcohols were not changed by this and could be isolated [6].



The dehydration of esters of β-acetoxy-α, β-dihydrogeranic acid (I, R'=$COCH_3$) by slow heating in the presence of catalytic amounts of anhydrous potassium acetate and subsequent reduction gave a mixture of nerol and geraniol (III, trans- and cis-), with a noticeably larger quantity of the first. By oxidizing with manganese dioxide, a mixture of stereoisomeric geranials (neral and geranial) (IV, trans- and cis-) was obtained in more than 90% yield. The mixture of semicarbazones (m. p. 130-135°) obtained from the aldehyde was chromatographed on aluminum oxide to give the separation of neral semicarbazone (m. p. 171-172°), that was easily washed out, and geranial semicarbazone (m. p. 162-165°), which was more strongly adsorbed, in a ratio of about 3.7 : 1. This proved that the isomerism of the dehydration products of esters of hydroxyacids lay not only in the position of the double bond formed but also in the steric position of the substituents around this bond.

Dehydration of (I), (R'=H) by heating with phosphorous oxychloride in a mixture of benzene and pyridine resulted in an ester, which when reduced gave an alcohol containing 15-17% of a β, γ-unsaturated isomer (VI) that manganese dioxide, as repeated investigations showed, could not oxidize. Dehydration of I (R'=H) by heating with phosphorus tribromide in the presence of pyridine and its subsequent reduction resulted in an alcohol in which the content of the β, γ-unsaturated isomer (VI) reached 40-45%. A mixture of aldehydes, giving a crystalline semicarbazone (m. p. 130-135°), was also obtained from that part of the alcohol which was oxidized by manganese dioxide. The semicarbazones were considerably more strongly adsorbed on the column during chromatography. Semicarbazones of neral (m. p. 171-172°) and geranial (m. p. 160-163°) were obtained after elution with a large quantity of chloroform. As can be seen from the table data, the amount of the "geranial" form of the geranic acid formed sharply increased by dehydrating with phosphorus halogen derivatives in the presence of pyridine.

The Results of Dehydration of Esters of β-Hydroxy-α, β-dihydrogeranic Acid

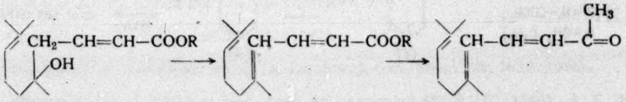
No. of sample	Reagent and dehydrogenation method	Content in % α,β-unsaturated isomer in the dehydration products	Ratio neral: geranial in the product of manganese dioxide oxidation
1	Pyrolysis of the acetyl derivative	~ 100	3.7 : 1
2	$POCl_3$ + pyridine	83-85	1 : 4
3	PBr_3 + pyridine	58-60	1 : 10

Thus, dehydration by heating the acetyl derivative resulted in esters of geranic acid mainly with a steric configuration that corresponded to nerol. The effect of phosphorus halogen derivatives led to the formation of esters of geranic acid and of a considerable quantity of the isomeric β, γ-unsaturated compounds; furthermore, in the α, β-unsaturated part of the esters obtained, the main isomers were those with the steric configurations corresponding to geraniol.

The difference in the steric configuration of α, β-unsaturated esters, obtained by acetate pyrolysis and the action of phosphorus halogen derivatives in the presence of pyridine indicated substitution halogenation with rotation of the configuration and subsequent splitting off of hydrogen halide elements.

Two factors determined the formation of α, β- and β, γ-unsaturated compounds during the course of dehydration: 1) the competing effect of the polar carboxyl group, which raises the proton lability of the neighboring carbon atom; 2) the specific action of the alkyl groups, which lower the activation energy of halogen derivatives for the elimination reaction – formation of ethylenes with the greatest number of alkyl substituents (Saïzeff's law) [8, 9].

The introduction of a vinyl group (IX) between the carboxyl and methylene group which it activates, changed the direction of the dehydration so that α, β- (more exactly, γ, δ-) isomers predominated [10]. This may have resulted from the increased effect of the carboxyl, due to its readily polarizable double bond, as well as the effect of the double bond itself, which enters into the configuration and promotes the formation of a second multiple bond. As a result mainly esters of 5,9-dimethyldecatrien-2,4,8-ic acid (X) were formed by the dehydration of esters of 5,9-dimethyldecadien-2,8-ol-5-ic-(1) acid (IX) with phosphorus tribromide or phosphorus oxychloride.



(IX) ($R=CH_3$, C_2H_5) (X) ($R=H$, CH_3, C_2H_5) (XI)

The steric direction, characteristic for dehydration with phosphorus halogen derivatives, is retained in this reaction as we had established. The mixture of stereoisomeric pseudoionones (XI), formed by saponification of ester (X), with subsequent treatment of the free acid with methyllithium, was converted to the 2,4-dinitrophenylhydrazones. Chromatography of the hydrazones on aluminum oxide showed the predominance of pseudoionone dinitrophenylhydrazone, corresponding to geraniol (m. p. 148-149°). The data obtained show that there is a relation between the formation of different amounts of stereoisomeric (cis-trans-)-forms and the position of the double bond formed in the hydrocarbon ring.

EXPERIMENTAL

1. Methyl esters of 3,7-dimethyloctadien-2,6-oic-(1) acid (geranic) (II, R=CH_3) and 3,7-dimethyloctadien-3,6-oic-(1) acid (V, R=CH_3). A solution of 16.2 g (0.8 moles) of the ethyl ester of β-hydroxy-α, β-dihydrogeranic acid (b. p. 108-110° at 3 mm) was added to a mixture of 12.7 g (0.472 moles) of phosphorus tribromide and 1.7 ml of pyridine with stirring and at 50-60°. Then a further 5 ml of pyridine was added and it was stirred at 50-60° for 30 minutes. The reaction mixture was cooled to 0°, 150 ml of water was added and it was extracted with ether. The extract was washed with dilute hydrochloric acid and a saturated aqueous solution of sodium bicarbonate and dried with sodium sulfate. The ether was evaporated off, the residue was distilled and the dehydration product was obtained as a colorless liquid. The yield was 10.8 g (73.5%).

B. p. 110-112° at 8 mm, n_D^{20} 1.4662, d_4^{20} 0.9248, MR_D 54.55. $C_{11}H_{18}O_2F_2$. Calculated 53.72.

The substance did not contain active hydrogen (Zerewitinov).

2. 3,7-Dimethyloctadien-2,6-ol-1 (III) and 3,7-dimethyloctadien-3,6-ol-1 (VI). 9.1 g of the mixture of esters obtained in experiment 1 was reduced in an ether medium with 2.2 g of lithium aluminum hydride at −30°. After distillation we obtained a colorless, mobile liquid. The yield of the mixture of isomeric alcohols was 6.4 g (89%), b. p. 98-100° at 3 mm.

Found %: act. H 0.628. $C_{10}H_{17}OH$. Calculated %: act. H 0.650.

3. 3,7-Dimethyloctadien-2,6-al (citral) (IV). 3.7 g of the mixture of isomeric alcohols from experiment 2 was shaken with a suspension of manganese dioxide in 150 ml of petroleum ether (b. p. 50-60°) for 3 hours. The manganese dioxide was filtered off, the solvent was distilled off and the residue was distilled in vacuum. A slightly yellow liquid with a characteristic smell was obtained. The yield was 2.3 g (78%) with b. p. 84-86° at 2 mm. The active hydrogen content was found to be 0.263%.

The material contained 40% of unoxidized 3,7-dimethyloctadien-3,6-ol-1 (VI).

4. Cis- and trans-3,7-dimethyloctadien-2,6-al-1. Geranial and neral (IV, cis- and trans-). A solution of 0.3 g of semicarbazide hydrochloride in 0.7 ml of water was mixed with a solution of potassium acetate in 0.5 ml of alcohol and added to a solution of 0.5 g of the oxidation product in 1 ml of alcohol. 0.45 g of slightly yellow crystals were filtered off and recrystallized from 1 ml of dry methanol. Citral semicarbazone (a mixture of the two isomers) was obtained. The yield was 0.38 g (55%) with m. p. 130-135°.

Found %: N 19.82. $C_{11}H_{19}ON_3$. Calculated %: N 20.09.

200 mg of the semicarbazone was dissolved in 2 ml of dry chloroform and put onto a column with 10 g of aluminum oxide (activity II, according to Brockmann). It was eluted with chloroform (400 ml). On evaporating the solvent, 12 mg of material was obtained. After recrystallization from methyl alcohol, the m. p. was 170-171°, which corresponds to neral semicarbazone. Elution with a mixture of 90 ml of chloroform and 10 ml of dry ethyl alcohol gave 123 mg of a semicarbazone. After recrystallization from methyl alcohol the m. p. was 162-163°, which corresponds to geranial semicarbazone.

5. Separation of the semicarbazones of the stereoisomeric citrals, obtained from the products of phosphorus oxychloride dehydration. 200 mg of the semicarbazone was dissolved in 2 ml of dry chloroform and put onto a column with 10 g of aluminum oxide (activity II). It was eluted with chloroform (350 ml) and then with a mixture of 90 ml of chloroform and 10 ml of dry ethyl alcohol. After distilling off the solvents from the first fraction we obtained 26 mg of material and from the second fraction, 107 mg. Recrystallization from methyl alcohol gave neral semicarbazone with m. p. 169-171° from the first eluate and geranial semicarbazone with m. p. 162-163° from the second.

6. The ethyl ester of 5,9-dimethyldecatrien-2,4,8-oic-(1) acid (X). Dehydration with phosphorus tribromide. A solution of 4.8 g of the ethyl ester of 5,9-dimethyldecadien-2,8-ol-5-oic-(1) acid (IX) (R=C_2H_5) in 2 ml of pyridine and 20 ml of benzene was added to a mixture 5.4 g phosphorus tribromide and 1 ml of pyridine with stirring and at 50-60°. Then a further 2 ml of pyridine was added and it was stirred at 50-60° for 30 minutes. The reaction mixture was cooled to 0°, 50 ml of water was added and it was extracted with ether. The ether-benzene extract was washed free from pyridine with dilute sulfuric acid and a saturated solution of sodium bicarbonate and dried with sodium sulfate. The solvent was evaporated off and the residue was distilled in vacuum. The yield of the ethyl ester of 5,9-dimethyldecatrien-2,4,8,-oic-(1) acid was 3.4 g (77%) with

b. p. 109-111° at 8 mm. The substance did not contain active hydrogen. λ_{max} 275 mμ, $E^{1\%}_{1\,cm}$ 508.

6,10-dimethylundecatrien-3,5,9-one-2 (pseudoionone) (XI). a) 5,9-Dimethyldecatrien-2,4,8-oic-(1) acid (X, R=H). 3 g of the ethyl ester of 5,9-dimethyldecatrien-2,4,8-oic-(1) acid was hydrolyzed with 12 ml of 10% alcoholic KOH solution for 2 hours at 60-70°. The acid was obtained as a yellow oily substance. The yield was 2.15 g (82%).

b) Pseudoionone. 2.0 g of 5,9-dimethyldecatrien-2,4,8-oic-(1) acid was treated with 60 ml of an ether solution of methyllithium (containing 0.65 g of methyllithium). A yellow, oily liquid was obtained with b. p. 95-96° at 0.6 mm. The yield of pseudoionone was 1.7 g (86%).

7. Preparation and chromatographic separation of the 2,4-dinitrophenylhydrazones of the synthetic pseudoionone. 5 ml of anhydrous alcohol was added to a solution of 1 g of 2,4-dinitrophenylhydrazine in 2 ml of sulfuric acid (d_4^{20} 1.84) and the reagent produced was added to 1 g of pseudoionone in 3 ml of dry alcohol. A red oily material was precipitated, which quickly crystallized, the precipitate was filtered off, washed with alcohol, dissolved in 3 ml of chloroform and 8 ml of methanol was added. After standing at −5° for 12 hours, the red crystals were filtered off. The yield of pseudoionone 2,4-dinitrophenylhydrazone was 1.3 g (70%) with m. p. 132-136°.

Found %: N 15.05. $C_{19}H_{24}O_4N_4$. Calculated %: N 14.83.

200 mg of the 2,4-dinitrophenylhydrazone was dissolved in 2 ml of dry chloroform and put onto a column with 20 g of aluminum oxide and eluted with chloroform. The material separated into two bands on the column, the upper one being more weakly colored. The intensely colored lower band was eluted by passing 50 ml of chloroform through; the second band was eluted with a mixture of 20 ml of chloroform and 20 ml of acetone. After evaporating off the solvents, the first eluate yielded crystals with m. p. 148-149°, which corresponded to the 2,4-dinitrophenylhydrazone of the pseudoionone from geranial. The yield was 175 mg. The second eluate gave a 2,4-dinitrophenylhydrazone with m. p. 118-119°, corresponding to the pseudoionone from neral. The yield was 21 mg.

Chromatographic separation of the 2,4-dinitrophenylhydrazones of pseudoionone from natural citral. 200 mg of the 2,4-dinitrophenylhydrazone was separated on aluminum oxide by the method above. We obtained 185 mg of a 2,4-dinitrophenylhydrazone with m. p. 148-149° and 12 mg of one with m. p. 118-119°.

SUMMARY

1. It was shown that dehydration of esters of 3,7-dimethylocten-6-ol-3-ic-(1) acid (β-hydroxy-α,β-dihydrogeranic) and 5,9-dimethyldecadien-2,8-ol-5-ic-(1) acids gave compounds with the double bond in the α, β- and β, γ-positions and with cis- and trans-substituents of the double bond.

2. It was found that pyrolysis of the acetyl derivatives of these acids gave mainly α, β-unsaturated compounds with a predominantly trans-(nerol) form. The action of phosphorus halogen compounds resulted in a mixture of compounds, containing double bonds in the α, β- and β, γ-positions. The α,β-unsaturated materials obtained thus were mainly of the cis-(geraniol) form.

3. The esters of unsaturated acids obtained were converted into alcohols, aldehydes, and ketones, which were identified with natural compounds or with their corresponding derivatives.

LITERATURE CITED

[1] O. Wallach, Ann. 360, 26 (1908); 365, 255 (1909).

[2] G. Kon and K. Nargund, J. Chem. Soc. 1932, 2461; H. Gilman, Organic Chemistry I, 1042 (1948).

[3] K. Bernhauer and R. Forster, J. prakt. Chem. 147, 199 (1936).

[4] C. A. Vodoc and H. Schinz, Helv. Chim. Acta 33, 1313 (1950).

[5] G. I. Samokhvalov, M. Miropolskaya, L. Vakulova, and N. A. Preobrazhensky, Proc. Acad. Sci. USSR 84, 1179 (1952).

[6] G. I. Samokhvalov, M. Miropolskaya, and N. A. Preobrazhensky, J. Gen. Chem. 26, 54 (1956) (T.p. 49).*

[7] F. Tiemann, Ber. 31, 3324(1898); 32, 117 (1899); 33, 877 (1900).

[8] A. Saizeff, Ann. 179, 296 (1875).

[9] M. Dhar, E. Huges, and C. Ingold et al., J. Chem. Soc. 1948, 2013.

[10] G. I. Samokhvalov, M. Miropolskaya, L. Vakulova, and N. A. Preobrazhensky, J. Gen. Chem. 25, 545 (1955) (T.p. 515).*

Received November 5, 1955

All-Union Institute for the Scientific Investigation
of Vitamins

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* T.p. = C. B. Translation pagination.

HETEROCYCLIC COMPOUNDS

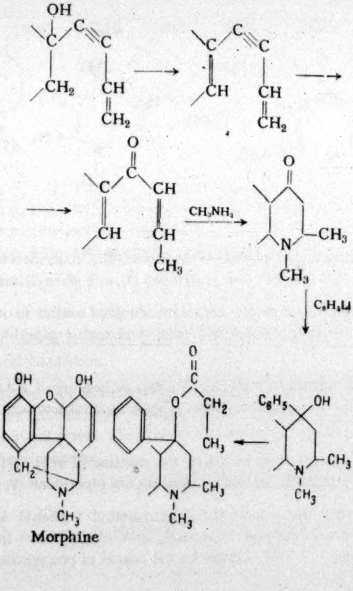
39. SYNTHETIC ANESTHETICS

IV. ESTERS OF 1, 2, 5-TRIMETHYL-4-PHENYL-4-PIPERIDOL WITH ALIPHATIC ACIDS

SYNTHESIS OF PROMEDOL AND ISOPROMEDOL

I. N. Nazarov, N. S. Prostakov and N. I. Shvetsov

γ-Piperidones, formed by the reaction of primary amines with divinyl ketones [1], obtained by the hydration of divinyl-acetylene hydrocarbons [2], were used by us for the synthesis of esters of 4-phenyl-4 piperidols, which possess extremely high anesthetic (analgesic) activity and according to their structure are a definite part of a morphine molecule.

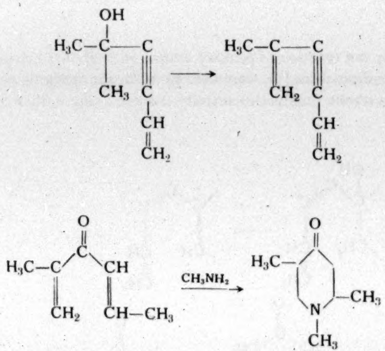


In the last few years, some investigators [3], using different methods for building up the piperidine ring, obtained a series of analogous compounds which in certain cases possess considerable anesthetic activity.

The use for this purpose of γ-piperidones, obtained from vinylethinylcarbinols, is especially interesting as all the stages of their synthesis proceed exceptionally simply and with high yields, while the wide selection of available starting vinylethinylcarbinols makes it possible to synthesize γ-piperidones with various substitutents in the piperidine ring.

Of the esters of 4-phenyl-4-piperidols obtained by us, the propionates of the stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols have an extremely high anesthetic (analgesic) effect, 2 to 10 times greater than that of morphine, and with relatively low toxicity. During the last seven years these compounds have been thoroughly studied in a number of pharmacological and medical institutions in the Soviet Union and are at present widely used in medical practice as highly effective anesthetics, under the name of "promedol" [4].

The starting 1,2,5-trimethyl-4-piperidone (I) was obtained by the reaction of methylamine with propenylisopropenyl ketone [1] which, in its turn, was obtained from the technically available dimethylvinylethinylcarbinol [5]:



(I)

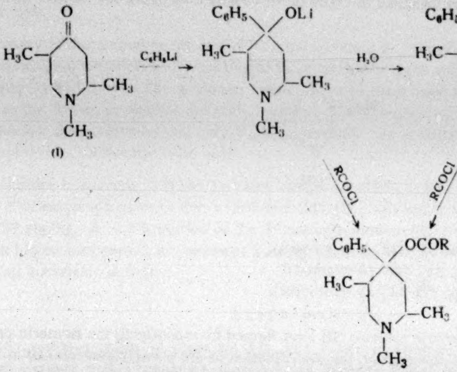
The stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols (II), described in one of the previous reports [6], were formed by treatment of 1, 2, 5-trimethyl-4-piperidone (I) with phenyllithium.

The corresponding esters (acetate and propionate) were obtained earlier in our laboratory by treating the high melting (m. p. 107-108°) stereoisomer of 1,2,5-trimethyl-4-phenyl-4-piperidol with acetic and propionic anhydrides [6].

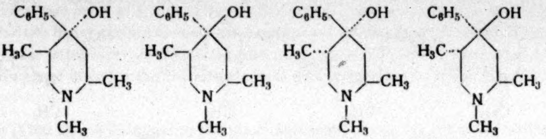
In this report we describe the synthesis of a series of esters of isomeric 1,2,5-trimethyl-4-phenyl-piperidols by the action of aliphatic acid halides on piperidols (II) in a benzene or chloroform medium, as well as without solvent.

Some esters were obtained in yields of up to 70% by the reaction of acid halides with the lithium alcoholate of 1,2,5-trimethyl-4-phenyl-4-piperidol, formed by treating the piperidone (I) with phenyllithium.

Of the four theoretically possible stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols (II), with different steric positions of the substitutents in the piperidine ring, up to now we have isolated only three geometric isomers (m. p. 106-107°, 102-103° and 107-108°) formed by the action of phenyllithium on piperidone (I) in a ratio of approximately 1 : 2 : 18.



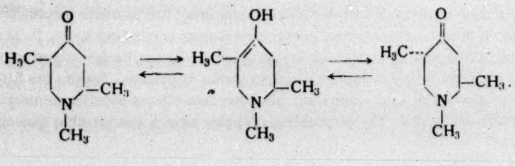
R = CH_3; C_2H_5 (IV); n-C_3H_7 (V); iso-C_3H_7 (VI); iso-C_4H_9 (VII);
$CH_2CH_2OCH_3$ (VIII); $CH_2CH_2OC_2H_5$ (IX); $CH_2CH_2OC_3H_7$ (X);
$CH_2CH_2OC_4H_9$ (XI).



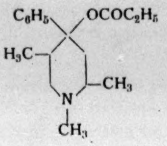
α-Isomer, m.p. 106-107°; hydrochloride, m.p. 233-235°; picrate, m.p. 182-183°.
β-Isomer, m.p. 102-103°; hydrochloride, m.p. 173-174°; picrate, m.p. 174-175°.
γ-Isomer, m.p. 107-108°; hydrochloride, m.p. 158-159°; picrate, m.p. 199-199.5°.

Apparently, the fourth steric isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) is not formed at all under the normal experimental conditions.

The fact that three of the four theoretically possible stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols (II) may be isolated shows that 1,2,5-trimethyl-4-piperidone (I) enters into reaction with phenyllithium in both of its stereoisomeric forms (cis and trans), and their ratio may differ considerably depending on the method of isolation and treatment of the piperidone:



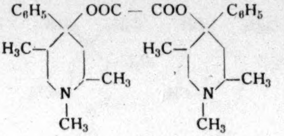
The stereoisomeric propionates (IV) corresponding to the three stereoisomers of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) isolated were obtained in yields of 70-90% by esterifying the isomers with propionyl chloride.



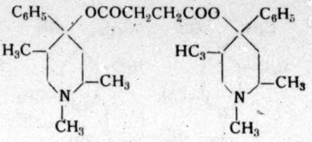
α-Isomer, hydrochloride, m. p. 227-229° (α-promedol);
β-Isomer hydrochloride, m. p. 182-183° (β-promedol).
γ-Isomer, hydrochloride, m. p. 222-223° (γ-promedol).

The corresponding stereoisomeric alcohols (II) were formed by saponifying the isomeric propionates (IV) with an alcoholic alkali solution. Consequently, the esterification of the phenylpiperidols (II) as well as the saponification of their corresponding esters (IV) takes place without any regrouping.

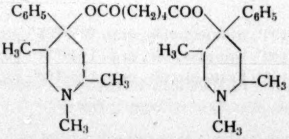
Esters of dibasic acids were also prepared by the action of the acid chloride on the lithium alcoholate of 1,2,5-trimethyl-4-phenyl-4-piperidol. The syntheses of the esters of oxalic, succinic and adipic acids, (XII), (XIII) and (XIV), were used as examples.



(XII)



(XIII)



(XIV)

The hydrochlorides of these esters are colorless crystalline materials which rapidly become wet in air. The hydrochloride of the oxalic ester (XII) is especially strongly hydroscopic, while the hydrochloride of the adipic ester (XIV) is considerably less hygroscopic.

Of the series of esters of 1,2,5-trimethyl-4-phenyl-4-piperidol, the isomeric propionates (IV) possess the highest anesthetic effect, according to data from physiological tests carried out by M. D. Mashkovsky et al.. in the pharmacological laboratories of the All-Union Institute for the Scientific Investigation of Pharmaceutical chemicals, and are among the strongest analgesic agents known at present. Besides the high activity the relatively low toxicity, the absence of habit-formation and other side effects peculiar to morphine, are important advantages of these synthetic analgesics. The propionates (IV) also have a considerable spasmolytic activity.

The stereoisomers of 1,2,5-trimethyl-4-phenyl-4-piperidol propionates (IV) also differ greatly from each other in their activity.

The activity of the γ-isomer (promedol) is approximately 2-3 times greater than the activity of morphine, while the β-isomer (isopromedol) with equal toxicity, is two times more active than promedol and exceeds morphine activity by 4-6 times. The α-isomer turned out to be even more active. It has an anesthetic effect twice as great as the β-isomer and has the same toxicity. The analgesic effect of the acetate of the γ-isomer (III) is 4-5 times less than promedol and only slightly exceeds the activity of demerol (the ethyl ester of 1-methyl-4-phenyl-4-piperidinecarboxylic acid).

The γ-isomer isobutyrate (VI) has the same anesthetic effect as promedol but exceeds it somewhat in toxicity. The β-alkoxypropionates of the γ-isomer (VIII), (IX), (X) and (XI) have no analgesic activity even in doses up to 20 mg/kg. A 0.5% solution of the β-butoxypropionate (XI) has only a weak anesthetic effect. The use of it in higher concentrations produces a strong effect on the mucous membrane. The adipic ester (XIV) also has no anesthetic activity.

EXPERIMENTAL

1,2,5-Trimethyl-4-phenyl-4-piperidol (II). a) 1.5 liters of absolute ether was placed in a three-necked flask fitted with a stirrer, reflux condenser, thermometer, dropping funnel and a gas inlet, and under a stream of nitrogen, 108 g of finely cut lithium, with the oxide layers cleaned off, was introduced. Then, under a continuous stream of nitrogen, 20 g of bromobenzene was added to the mixture and after the beginning of an intensive reaction, a solution of 1200 g of bromobenzene in 1 liter of absolute ether was added dropwise at such a rate that the ether boiled continuously. At the end of the bromobenzene addition, the reaction mixture was stirred while the ether boiled for an hour and a half until the lithium completely dissolved. 902 g of 1,2,5-trimethyl-4-piperidone (I) (b.p. 73-75° at 7 mm) in 1 liter of absolute ether was added dropwise to the solution of phenyllithium obtained over two hours at 5-10°. The reaction mixture was left overnight, then stirred at the boiling point of the ether for two hours, cooled to room temperature and hydrolyzed with water (900 ml). The ether layer was separated, the water layer was extracted with ether, the ether extracts were dried with magnesium sulfate and after distillation of the ether the volatile products were evaporated in vacuum at 10 mm on a boiling water bath.

The residue (1200 g) was dissolved in 150 ml of hot benzine (b.p. 80-120°), the solution was cooled and left overnight. The next day there had separated 268 g of the high melting γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) with m.p. 107-108° (from benzine) which did not depress the melting point of a sample described earlier [6]. The hydrochloride of this isomer melted at 158-159° (from acetone) and the picrate melted at 199-199.5° (from alcohol). By partially evaporating down the mother liquor in vacuum and introducing a seed of the γ-isomer, a further 167 g of this material with m. p. 107-108° was isolated. The uncrystallized oil was distilled in vacuum: 1st fraction b.p. 105-111° (1 mm) 58 g; 2nd fraction b.p. 111-180° (1 mm) 587 g.

The 1st fraction was dissolved in benzine and saturated with dry hydrogen chloride. The precipitate of hydrochlorides was extracted with hot, dry acetone. This yielded 5.3 g of the hydrochloride of the α-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) with m.p. 233-235°, which was insoluble in acetone. The free base of the low melting α-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) was prepared from the hydrochloride by treatment with ammonia and melted at 106-107° (from benzine).

Found %: N 6.34, 6.40. $C_{14}H_{21}ON$. Calculated %: N 6.40.

The picrate of this isomer melted at 182-183° (from alcohol).

The acetone solution of the hydrochlorides was evaporated in vacuum, the residue was dissolved in water and treated with ammonia. After several recrystallizations of the precipitate from benzine, we obtained 5.8 g of the β-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) with m.p. 102-103°.

Found %: N 6.41, 6.45. $C_{14}H_{21}ON$. Calculated %: N 6.40.

The hydrochloride of the β-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol melted at 173-174° (from alcohol and acetone) and the picrate melted at 174-175° (from alcohol).

By the addition of 80 ml of benzine and a seed of the γ-isomer, 14.6 g of crystals with m.p. 107-108° were obtained from the 2nd fraction (b.p. 111-180° at 1 mm). The introduction of a seed of the β-isomer into the mother liquor gave 17.9 g of crystals with m.p. 95-98°, which melted at 102-103° after recrystallization from benzine and did not depress themelting point of the sample of β-isomer described above.

The uncrystallizable oil was again distilled in vacuum: 1st fraction 110-119° (0.2 mm), 176.6 g; 2nd fraction 119-130° (0.2 mm), 189.1 g; 3rd fraction 130-140° (0.2 mm), 39.7 g; residue in flask 130 g.

By seeding, 26.4 g of the high melting γ-isomer with m.p. 107-108° was isolated from the 2nd fraction and from the first fraction we isolated 22.3 g of the β-isomer with m.p. 102-103° and 18 g of the γ-isomer with m.p. 107-108°.

The uncrystallizable residues were combined and again distilled in vacuum. A fraction with b.p. 116-127° (0.2 mm) was dissolved in benzine and saturated with hydrogen chloride and the precipitate was recrystallized from alcohol to give 26.6 g of the hydrochloride of the γ- isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) with m.p. 233-235°.

In all, we obtained from this experiment: 494 g of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol with m.p. 107-108°, 46 g of the β-isomer with m.p. 102-103° and 28 g of the α-isomer with m.p. 106-107°. About 450 g of material was left as an inseparable mixture of isomers of 1,2,5-trimethyl-4-phenyl-4-piperidol.

b) 100 g of 1,2,5-trimethyl-4-piperidone (b.p. 80-82° at 5 mm) was gradually added to phenylmagnesium bromide, prepared from 24 g of magnesium and 157 g of bromobenzene in 350 ml of absolute ether, cooled to 0°. The reaction mixture was stirred for 1 hour at room temperature, and on the following day it was hydrolyzed with 200 ml of water. The product was extracted with ether and distilled in vacuum on a boiling water bath. Thus we obtained 80 g of the original 1,2,5-trimethyl-4-piperidone and 25 g of an oily residue, which was dissolved in 10% hydrochloric acid.

To separate the neutral materials, the hydrochloric acid solution was treated with three portions of isooctane (30 ml) and then, to separate the free base, concentrated ammonia solution. The oil thus separated was partially crystallized by adding isooctane. We obtained 3.3 g of the γ-isomer of 1,2,5-trimethyl-4-phenyl-piperidol (II) with m.p. 104-107°. The mother liquor was distilled in vacuum to give 3 g of a viscous liquid with b.p. 140-145° (5 mm),which, after addition of isooctane and subsequent crystallization, yielded a further 1 g of the γ-isomer of (II) with m.p. 105-107° and 0.13 g of the β-isomer of (II) with m.p. 97-100°. We also isolated from the remaining mother liquors 0.05 g of the hydrochloride of the α-isomer of (II) with m.p. 230-231°.

All the isomers of 1,2,5-trimethyl-4-phenyl-4-piperidol isolated failed to depress the melting points of the corresponding samples described above.

The propionate of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (promedol). a) 177 g of the high melting γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) with m.p. 107-108° was gradually added to 186 g of freshly distilled propionyl chloride, which was continuously stirred and cooled with cold water. The piperidol completely dissolved and the yellow solution was heated for 10 hours at 80°. At the end of the heating, 50 ml of benzene was added to the reaction mixture. On cooling the mixture in ice and salt, the contents of the flask crystallized. The crystals were filtered off and washed on the filter with small portions of benzene. After recrystallization from acetone, we obtained 140 g of the hydrochloride of γ-1,2,5-trimethyl-4-phenyl-4-piperidol propionate (IV), which melted at 222-223°.

Found %: C 65.76, 65.80; H 8.01, 8.04; N 4.31, 4.73; Cl 11.35, 11.43. $C_{17}H_{26}O_2NCl$.
Calculated %: C 65.49; H 8.34; N 4.48; Cl 11.40.

b) 30 g of the high melting γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m. p. 107-108°) was gradually added to 38 g of propionyl chloride and the solution was allowed to stand for 10 days at room temperature. The crystalline precipitate was filtered off and washed on the filter with small portions of acetone.

We obtained 25.2 g of the hydrochloride of γ-1,2,5-trimethyl-4-phenyl-4-piperidyl propionate (IV), which melted, like the previous sample, initially at 199-200° and then, at the second melting, at 221-222°. On working up the same experiment after 1 day, we obtained 14 g of the promedol.

c) 10 g of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 107-108°), 13 ml of propionic anhydride and 10 ml of pyridine, dried over calcium oxide, were heated 2 hours at 160° and 8 hours at 180°. Excess propionic anhydride and the pyridine were distilled off in vacuum, the residue was dissolved in water and treated with soda and the base was isolated by an ether extraction. After drying and distilling off the ether, the reaction product was distilled in vacuum. We obtained 11 g of the base as a viscous liquid with b.p. 115-134° (0.5 mm), which was converted into the hydrochloride by passing dry hydrogen chloride through its ether solution. The precipitate thus obtained was boiled for half an hour with 30 ml of dry acetone and after cooling was filtered and dried. We obtained 11.5 g of the hydrochloride of γ-1,2,5-trimethyl-4-phenyl-4-piperidyl propionate with m.p. 222°.

The compound described was subjected to a full pharmacological and clinical investigation and at the present time it is widely used under the name of "promedol" as a new anesthetic with 2-3 times the activity of morphine.

The picrate of γ-1,2,5-trimethyl-4-phenyl-piperidyl propionate melted at 171-172° (from alcohol), the iodomethylate melted at 214-214.5° (from alcohol), the tartrate melted at 167-168° (from alcohol) and the chlorobenzylate softened in the range 158-161°, then solidified and melted at 200-202° (several recrystallizations from alcohol-acetone).

The propionate of the β-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (isopromedol). 22 ml of freshly distilled propionyl chloride was added to a solution of 22 g of the β-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) with m.p. 102-103° in 15 ml of chloroform. The solution was allowed to stand overnight and next day the precipitate was filtered off, washed with chloroform and recrystallized from a mixture of acetone and alcohol. We obtained 20.5 g of the hydrochloride of β-1,2,5-trimethyl-4-phenyl-4-piperidyl propionate (IV) with m.p. 182-183°.

Found %: C 65.53, 65.71; H 7.98, 7.95; N 4.37, 4.46. $C_{17}H_{26}O_2NCl$.
Calculated %: C 65.49; H 8.34; N 4.48.

The compound described, known as "isopromedol", was subjected to detailed pharmacological and clinical investigation and proved to be an extremely strong analgesic with 4-6 times the activity of morphine and approximately twice the activity of promedol at the same toxicity. Isopromedol is one of the strongest and most interesting analgesics known at the present time.

The propionate of the α-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol. 1.7 g of the α-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) was dissolved in 10 ml of benzene. 2.1 ml of propionyl chloride was added to the solution. On the following day the precipitate (2.4 g) was filtered off, washed several times with benzene and dried. Recrystallization of the precipitate from acetone yielded 0.7 g of a material with m.p. 101-108°, which according to analysis corresponded to the hydrochloride of 1,2,5-trimethyl-4-phenyl-4-piperidyl propionate.

Found %: N 4.41, 4.57. $C_{17}H_{26}O_2NCl$. Calculated %: N 4.48.

From the mother liquor we obtained 0.4 g of the hydrochloride of α-1,2,5-trimethyl-4-phenyl-4-piperidyl propionate (IV) with m.p. 227-229°.

Found %: N 4.31, 4.32. $C_{17}H_{26}O_2NCl$. Calculated %: N 4.48.

The action of propionyl chloride on the lithium alcoholate of 1,2,5-trimethyl-4-phenyl-4-piperidol.

a) The lithium alcoholate was prepared as described above from 20.7 g of lithium, 280 g of bromobenzene and 175 g of 1,2,5-trimethyl-4-piperidone in 400 ml of absolute ether. Then 265 g of propionyl chloride, dissolved in 200 ml of absolute ether, was added from a dropping funnel over two hours, while the reaction mixture was vigorously stirred and the flask was cooled in ice water. Stirring was continued at room temperature for 1 hour and then for 3 hours at the boiling point of the ether. 500 ml of water was gradually added to the reaction mixture with vigorous stirring and the aqueous layer was separated and treated with soda until it was completely saturated. The free base was extracted with ether, dried with sodium sulfate and distilled in vacuum. We obtained 225 g of a mixture of stereoisomeric propionates of 1,2,5-trimethyl-4-phenyl-4-piperidol (IV) as a viscous, pale yellow liquid.

B. p. 139-141° (2.5 mm), n_D^{18} 1.5182, d_{18}^{18} 1.0319, MR 80.78; calc. 80.50.

Found %: C 74.52, 74.20; H 9.00, 8.78. $C_{17}H_{25}O_2N$. Calculated %: C 74.18; H 9.09.

There was a lower boiling fraction (b.p. 96-139° at 2.5 mm) of 10.2 g. The residue after distillation was 76.5 g.

A stream of dry hydrogen chloride was passed into a solution of the 225 g of propionates of 1,2,5-trimethyl-4-phenyl-4-piperidol obtained in 300 ml of dry ether. The precipitate of hydrochlorides was filtered off, washed with ether on the filter and quickly recrystallized from anhydrous alcohol. (On storage in air, the product became noticeably wet and deliquesced). The alcohol solution was heated with activated charcoal, filtered and stood for 3 hours in ice-salt cooling mixture. The fine granular precipitate of the hydrochlorides was filtered off and washed on the filter with three portions of anhydrous alcohol.

We obtained 30 g of crystals with m.p. 189-193°. After a second recrystallization from alcohol, we obtained 65 g of hydrochloride, which melted at 198-199°, but on further heating solidified again and then melted at 212-216°. Subsequent recrystallization of this hydrochloride gave a substance with m.p. 222-223°, which was identical with promedol.

b) The phenyllithium was prepared from 30 g of lithium, 223 g of bromobenzene and 1500 ml of ether. The precipitate of lithium bromide and unreacted metallic lithium was filtered off from the reaction mixture on a glass wool filter in an atmosphere of dry nitrogen. Then 180 g of 1,2,5-trimethyl-4-piperidone was added to the solution of phenyllithium obtained and next day 237 g of propionyl chloride. The propionyl chloride was run in at such a rate that the ether boiled vigorously all the time. This produced a voluminous colorless precipitate. After adding all the propionyl chloride, the reaction mixture was stirred vigorously for a further 2 hours while the ether boiled. The product was hydrolyzed with water (250 ml), the ether layer, containing the neutral products, was separated and the aqueous layer was treated with soda in the presence of ether. The base was extracted with five portions of ether of 200 ml each. The ether solution was dried with baked sodium sulfate, the ether was distilled off and the product was distilled in vacuum. We obtained 253 g of a mixture of stereoisomeric propionates of 1,2,5-trimethyl-4-phenyl-4-piperidol (IV) with b.p. 136-142° (3 mm). The material was dissolved in 300 ml of dry benzene, and 90 g of propionyl chloride was gradually added to the solution. The reaction mixture heated up considerably and became red. On cooling, crystals were gradually deposited from the solution. After 10 hours, the crystalline precipitate formed (146 g) was filtered off and washed several times on the filter with benzene. After distillation of the solvent and addition of soda solution, the mother liquor again yielded free base (113 g) with b.p. 135-140°, from which an additional 19 g of crystalline hydrochloride was obtained by treatment with propionyl chloride (40 g). The combined hydrochlorides (165 g) were recrystallized from a mixture of acetone and alcohol. We obtained 151 g of the hydrochloride of γ-1,2,5-trimethyl-4-phenyl-4-piperidyl propionate (promedol) as colorless crystals with m.p. 221-222°.

Hydrolysis of γ-1,2,5-trimethyl-4-phenyl-4-piperidyl propionate (promedol). 1.5 g of the hydrochloride of γ-1,2,5-trimethyl-4-phenyl-4-piperidyl propionate (IV) with m.p. 221-222° and 20 ml of 10% alcoholic caustic potash solution were boiled together for 3 hours. The alcohol was distilled off under reduced pressure and the piperidol formed by hydrolysis was extracted with ether. The ether solution was dried, the ether distilled off and the residue recrystallized from benzine to give 1 g of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) with m.p. 107-108°.

Hydrolysis of β-1,2,5-trimethyl-4-phenyl-4-piperidyl propionate (isopromedol). For the reaction we used 1.1 g of the hydrochloride of β-1,2,5-trimethyl-4-phenyl-4-piperidyl propionate (IV) with m.p. 182-183° and 25 ml of 10% alcoholic caustic soda solution. The reaction was carried out as described above. We obtained 0.65 g of the β-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (II) with m.p. 102-103° (from benzine).

The acetate of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (III). a) 10 ml of acetyl chloride was added to a solution of 10 g of the high melting γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 107-108°) in 20 ml of benzene. There was considerable heat evolved and a precipitate formed. After 10 minutes the precipitate completely dissolved and the solution became pale yellow. After standing for 10 hours at room temperature, the reaction mixture was heated for 2 hours at 80°. On cooling, crystals separated, which were filtered off and washed several times with benzene on the filter. We obtained 6.9 g of the hydrochloride of γ-1,2,5-trimethyl-4-phenyl-4-piperidyl acetate (III), which melted at 223-224° after recrystallization from a mixture of acetone and alcohol.

Found %: N 4.78, 4.71; Cl 11.89, 11.96. $C_{16}H_{24}O_2NCl$. Calculated %: N 4.71; Cl 11.93.

b) The lithium alcoholate of 1,2,5-trimethyl-4-piperidol was prepared from 3.63 g of metallic lithium, 45 g of bromobenzene and 30 g of freshly distilled 1,2,5-trimethyl-4-piperidone in 200 ml of absolute ether. The next day 37 g of acetyl chloride was added over 1.5 hours with vigorous stirring and cooling. Then the mixture was stirred at room temperature for 2 hours and 5 hours at the boiling point of the ether. The reaction produced a voluminous, crystalline precipitate, which grew under the ether, was filtered off, washed twice on the filter with ether and dissolved in water. Ether was added to the aqueous solution and the product was treated with soda with vigorous shaking.

The ether extract was dried over baked sodium sulfate and the product was distilled in vacuum to give 32.5 g of a mixture of acetates of the stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols (III) as a viscous yellow liquid with b.p. 130-132° (3.5 mm), n_D^{20} 1.5285.

Found %: C 73.46, 73.60; H 8.70, 8.59; N 5.63, 5.48. $C_{16}H_{23}O_2N$. Calculated %: C 73.56; H 8.81; N 5.37.

The acetates obtained were dissolved in 200 ml of absolute ether and dry hydrogen chloride was passed through the solution. This gave a colorless, crystalline precipitate of hydrochlorides, which, on separating off from the ether, quickly became wet in air and turned into an oil. The hydrochlorides were dissolved in absolute alcohol and the alcohol solution was boiled with active charcoal on a boiling water bath for half an hour under a reflux condenser fitted with a calcium chloride tube. After separation of the charcoal, the alcohol solution was evaporated to dryness in vacuum. Absolute ether was added to the residue and the mass was carefully ground. The crystalline precipitate formed was recrystallized from absolute alcohol. We obtained 16.1 g of the hydrochloride of the acetate (III), described above, as fine, granular, colorless crystals with m.p. 222-223°.

It was not possible to crystallize anything else out from the mother liquor remaining after the separation of the first portion of the hydrochloride. Therefore, the hydrochloride was again converted into the free base, which was distilled in vacuum and treated with hydrogen chloride (in ether). In this way we isolated an additional 5.2 g of the hydrochloride of the acetate (III) with m.p. 221-222°.

The picrate of γ-1,2,5-trimethyl-4-phenyl-4-piperidyl acetate melted at 171.5-172.5° after two recrystallizations from absolute alcohol.

Found %: N 11.53, 11.48. $C_{22}H_{26}O_9N_4$. Calculated %: N 11.43.

The butyrate of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (V). a) 3.5 g of butyryl chloride (b.p. 100-101°) was added to a solution of 3 g of the γ isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 207-208°) in 3.5 ml of anhydrous benzene. The dark solution was left until the next day. The precipitate was filtered off, washed with benzene on the filter and recrystallized from acetone. We obtained 0.7 g of the hydrochloride of γ-1,2,5-trimethyl-4-phenyl-4-piperidyl butyrate (V) with m.p. 209-210°.

Found %: N 4.38, 4.44. $C_{18}H_{28}O_2NCl$. Calculated %: N 4.30.

b) We reacted 2.7 g of lithium, 34 g of bromobenzene, 25 g 1,2,5-trimethyl-4-piperidone and 200 ml of absolute ether. 22.8 g of butyrl chloride in 70 ml of ether was added to the lithium alcoholate solution obtained. The reaction mixture was stirred for 1 hour at room temperature and for 2 hours at the boiling point of the ether. After working up in the usual way we obtained 23.9 g of the base as an oily liquid with b.p. 135-137° (2.5 mm).

Butyryl chloride (8.3 g) was added to a solution of 18.6 g of the base in 30 ml of dry benzene and the mixture was left for two days. The crystalline precipitate was washed with benzene and acetone and recrystallized from a mixture of alcohol and acetone. We obtained 8 g of the hydrochloride of γ-1,2,5-trimethyl-4-phenyl-4-piperidyl butyrate (V) with m.p. 207-209°, which did not depress the melting point of the sample described above.

The isobutyrate of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (VI). To prepare the lithium alcoholate of 1,2,5-trimethyl-4-phenyl-4-piperidol, we used 2.2 g of metallic lithium, 30 g of bromobenzene, 21 g of 1,2,5-trimethyl-4-piperidone and 200 ml of absolute ether. On the following day 300 ml of ether was added to the lithium alcoholate formed, and, over a period of three hours, 33 g of isobutyryl chloride (b.p. 92°) was run in with vigorous stirring and cooling of the flask in ice water. After working up in the usual way and vacuum distilling the base isolated, we obtained 27 g of a mixture of isobutyrates of the stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols (VI) as a viscous yellow liquid with b.p. 132-136° (2.5 mm). A picrate was prepared from this mixture, which melted at 190-192° after recrystallization from alcohol.

Found %: N 11.23, 10.91. $C_{24}H_{30}O_9N_4$. Calculated %: N 10.81.

The hydrochloride of 1,2,5-trimethyl-4-phenyl-4-piperidyl isobutyrate was prepared by passing dry hydrogen chloride into an ether solution of the base. This precipitated an oil, which was converted into strongly hygroscopic crystals by drying in a desiccator. Several recrystallizations from acetone gave a hydrochloride as unhygroscopic, colorless crystals with m.p. 209-210°.

Found %: N 4.60, 4.75. $C_{18}H_{28}O_2NCl$. Calculated %: N 4.30.

The isovalerate of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (VII). The isovalerate (VII) was prepared by treating the lithium alcoholate of 1,2,5-trimethyl-4-phenyl-4-piperidol with isovaleryl chloride. For the reaction we used 2.5 g of lithium, 27 g of bromobenzene, 19 g of 1,2,5-trimethyl-4-piperidone, 250 ml of absolute ether and 20 g of isovaleryl chloride.

The base isolated was distilled in vacuum to give the following fractions: 1st 41-45° (4 mm), 3 g; 2nd 110-135° (2.5 mm), 3 g; 3rd 135-137° (2.5 mm), 10 g; 4th 137-155° (2.5 mm), 1.5 g; residue 27.8 g.

5 g of isovaleryl chloride was added to a solution of 10 g of the 3rd fraction in 9 ml of dry benzene. The solution stood for 5 days, after which it was diluted with ether and the precipitate produced was recrystallized from acetone. We obtained 2.2 g of the hydrochloride of γ-1,2,5-trimethyl-4-phenyl-4-piperidyl isovalerate (VII) as colorless crystals with m.p. 213.5-214°.

Found %: N 4.09, 4.17. $C_{19}H_{30}O_2NCl$. Calculated %: N 4.12.

The β-methoxypropionate of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (VIII). 5 g of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 107-108°), 10 ml of dry benzene, 10 g of β-methoxypropionyl chloride (b.p. 134-136°) and 0.2 g of magnesium turnings were heated at 80-85° for 12 hours. Excess β-methoxypropionyl chloride and the benzene were distilled off in vacuum and the residual oily mass was washed with ether and dissolved in water. The aqueous solution was treated with soda and the oily layer of the free base, which separated, was extracted with ether, dried with sodium sulfate and, after removal of the ether, distilled in vacuum. We obtained 2.6 g of 1,2,5-trimethyl-4-phenyl-4-piperidyl β-methoxypropionate (VIII) as an oily liquid with b.p. 141-143° (2 mm).

The hydrochloride of the β-methoxypropionate (VIII) was colorless crystals with m.p. 168.5-170° (after three recrystallizations from absolute alcohol).

Found %: N 4.18, 4.27. $C_{18}H_{28}O_3NCl$. Calculated %: N 4.09

The β-ethoxypropionate of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (IX). A mixture of 7.2 g of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m. p. 107-108°), 15 ml of benzene, 15 ml of β-ethoxypropionyl chloride (b.p. 146-148°) and 0.3 g of magnesium was heated at 80-85° for 8 hours. The reaction product was worked up as in the previous experiment. By distillation of the free base in vacuum, we obtained 3.8 g of 1,2,5-trimethyl-4-phenyl-4-piperidyl β-ethoxypropionate (IX) as an oily liquid with b.p. 158-161° (2.5 mm). Besides this we obtained 1.8 g of a fraction with b.p. 118-124° (2.5 mm). The tarry residue was 1.5 g.

The hydrochloride of 1,2,5-trimethyl-4-phenyl-4-piperidyl β-ethoxypropionate was colorless crystals with m.p. 152-153° (from acetone).

Found %: N 4.39, 4.25; Cl 10.25. $C_{19}H_{30}O_3NCl$. Calculated %: N 3.94; Cl 10.01.

The β-propoxypropionate of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (X). For the reaction we used 6 g of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 107-108°), 12 ml of benzene, 12 ml of β-propoxypropionyl chloride (b.p. 73-75° at 35 mm) and 0.25 g of magnesium turnings. The reaction was carried out as described above. We obtained 3.5 g of 1,2,5-trimethyl-4-phenyl-4-piperidyl β-propoxypropionate (X) as an oily liquid with b.p. 154-158° (2 mm). We also obtained 2.3 g of a head fraction with b.p. 97-154° (2 mm) and a distillation residue of 0.8 g.

The hydrochloride of 1,2,5-trimethyl-4-phenyl-4-piperidyl β-propoxypropionate was colorless crystals with m.p. 173-175° (from acetone).

Found %: N 4.09, 4.24. $C_{20}H_{32}O_3NCl$. Calculated %: N 3.79

The β-butoxypropionate of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (XI). In the reaction we used 6.5 g of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 107-108°), 13 ml of dry benzene, 13 ml of β-butoxypropionyl chloride (b.p. 85-87° at 35 mm) and 0.25 g of magnesium. The reaction was carried out as described above. We obtained 3.6 g of 1,2,5-trimethyl-4-phenyl-4-piperidyl β-butoxypropionate (XI) as a thick, viscous liquid with b.p. 173-176° (2 mm).

The hydrochloride was colorless crystals with m.p. 154-155.5° (from acetone).

Found %: N 4.01, 3.85. $C_{21}H_{34}O_3NCl$. Calculated %: N 3.68.

The oxalic ester of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (XII). The esters of dibasic acids were prepared by the method used for the synthesis of esters of monobasic acids with the lithium alcoholate of 1,2,5-trimethyl-4-phenyl-4-piperidol.

In the reaction we used 1.1 g of metallic lithium, 15 g of bromobenzene, 10 g of 1,2,5-trimethyl-4-piperidone and 5 g of oxalyl chloride (b.p. 62-64°). At the end of the reaction, the mixture was treated with 15% hydrochloric acid until acid to litmus, and then with water until all the reaction mixture dissolved.

The aqueous layer was separated from the ether layer, which contained the neutral substances, and treated with soda in the presence of ether. Hydrogen chloride was passed into the ether extract of the basic products after it had first been dried with baked sodium sulfate. We obtained 4.1 g of the hydrochloride of 1,2,5-trimethyl-4-phenyl-4-piperidyl oxalate (XII), which, after boiling with activated charcoal in absolute alcohol and subsequent precipitation with ether, was a colorless, strongly hygroscopic material, which deliquesced in air.

Found %: Cl 12.18, 12.58. $C_{30}H_{42}O_4N_2Cl_2$. Calculated %: Cl 12.57.

The succinic ester of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (XIII). In the reaction we used 1.1 g of metallic lithium, 14.8 g of bromobenzene, 10 g of 1,2,5-trimethyl-4-piperidone and 6.1 g of succinyl chloride (b.p. 70-71° at 8.5 mm). The reaction was carried out as in the previous experiment.

The hydrochloride of the succinyl ester (XIII) was prepared by passing hydrogen chloride through an ether solution of the base and was purified by boiling with active charcoal in absolute alcohol and subsequent precipitation of the hydrochloride from the alcohol solution with absolute ether.

In this way we obtained 8.2 g of the pure hydrochloride of 1,2,5-trimethyl-4-phenyl-4-piperidyl succinate (XIII), which was colorless crystals, which became damp in air but to a noticeably lesser extent than the corresponding hydrochloride of the oxalic ester. On melting in a sealed capillary, it began to soften at 52° and at 58° the whole mass foamed up.

Found %: N 5.23, 5.05. $C_{32}H_{46}O_4N_2Cl_2$. Calculated %: N 4.72.

The adipic ester of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (XIV). In the reaction we used 1.25 g of lithium, 17 g of bromobenzene, 10 g of 1,2,5-trimethyl-4-piperidone and 6 g of adipyl chloride (b.p. 123° at 14 mm). The reaction and the working up of the products were carried out as described for the previous experiments.

On passing hydrogen chloride into an ether solution of the free base, a voluminous, colorless crystalline precipitate was formed, which, however, quickly deliquesced in air. The hydrochloride was precipitated in two ways. After passing hydrogen chloride for a short time, we obtained 13.5 g of a hydrochloride, which, after working up as described in the previous experiments, gave colorless crystals melting at 76° with vigorous foaming. It was considerably more stable in air than the hydrochloride of the oxalic ester and became noticeably moist only after several hours.

Found %: N 4.38, 4.36; Cl 11.05, 11.26. $C_{34}H_{50}O_4N_2Cl_2$. Calculated %: N 4.50; Cl 11.43.

After separating the first portion of hydrochloride, the residual ether solution was again treated with dry hydrogen chloride. This gave 12.7 g of hydrochloride with m.p. 81-83° (frothing), which, as indicated by analysis, was largely the half ester of adipic acid and 1,2,5-trimethyl-4-phenyl-4-piperidol.

Found %: Cl 9.81, 9.73. $C_{20}H_{30}O_4NCl$ Calculated %: Cl 9.26.

SUMMARY

The preparation of esters of stereoisomeric 1,2,5-trimethyl-4-piperidols with various aliphatic acids is described. Some of these esters, especially the propionates, have extremely high anesthetic activity and are some of the strongest analgesics now known.

We describe the synthesis of promedol and isopromedol which are most interesting analgesics, outstanding in anesthetic activity and relatively low toxicity.

LITERATURE CITED

[1] I. N. Nazarov and V. A. Rudenko, Bull. Acad. Sci. USSR, Div. Chem. Sci. 1948, 610.

[2] I. N. Nazarov et al., Bull. Acad. Sci. USSR, Div. Chem. Sci. 1941, 211; 1942, 200; 1946, 529, 633; 1947, 51, 205, 277, 253.

[3] O. Eisleb, O. Schauman, Deutsch. Med. Wochschr. 65, 961 (1939); Ziering et al. , J. org. Chem. 12, 894, 904, 911, (1947); H. Kägi, K. Miescher, Helv. Chim. Acta 32, 2489 (1949).

[4] I. N. Nazarov, M. D. Mashkovsky et al., Clinical Medicine 8, 60 (1952).

[5] I. N. Nazarov, Bull. Acad. Sci. USSR, Div. Chem. Sci. 1938, 683.

[6] I. N. Nazarov et al., Bull. Acad. Sci. USSR, Div. Chem. Sci. 1949, 5, 504.

M. V. Lomonosov Institute of
Fine Chemical Technology, Moscow

Received August 22, 1956.

HETEROCYCLIC COMPOUNDS

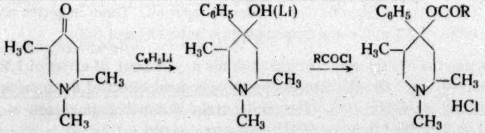
40. SYNTHETIC ANESTHETICS

V. ESTERS OF 1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDOL WITH AROMATIC ACIDS

I. N. Nazarov, N. S. Prostakov, N. N. Mikheeva and O. A. Shavrygina

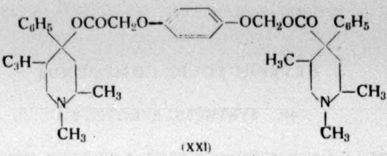
The previous report [1] described the esterification of stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols with various aliphatic acids and it was shown that some of the esters, especially the propionates obtained, possess exceptionally high anesthetic (analgesic) activity, exceeding that of morphine by several times (promedol, isopromedol). It seemed interesting to carry out the esterification of 1,2,5-trimethyl-4-phenyl-4-piperidol also with various aromatic acids to test their physiological activity, as it is known that the esters of amino alcohols with aromatic acids have an anesthetic effect (cocaine, novocaine).

The esterification of the high melting γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 107-108°) was carried out with acid halides in benzene at a temperature of 60-75° for 3-8 hours, to obtain the hydrochlorides of the corresponding esters in yields of up to 80%. Some esters were also prepared by the action of the acid chloride on the lithium alcoholate of 1,2,5-trimethyl-4-phenyl-4-piperidol, which was formed by treating 1,2,5-trimethyl-4-piperidone with phenyllithium.



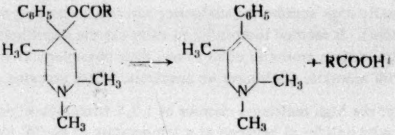
By this method the esters of the more accessible high melting γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 107-108°) with the following acids were obtained: benzoic (I), p-methylbenzoic (II), p-chlorobenzoic (III), p-bromobenzoic (IV), o-methoxybenzoic (V), p-methoxybenzoic (VI), p-nitrobenzoic (VII), p-aminobenzoic (VIII), phenylacetic (IX), cinnamic (X), hydrocinnamic (XI), cyclohexylcarboxylic (XII), phenoxyacetic (XIII), p-methylphenoxyacetic (XIV), o-methylphenoxyacetic (XV), o-methoxyphenoxyacetic (XVI), p-chlorophenoxyacetic (XVII), o-chlorophenoxyacetic (XVIII), o,p-dichlorophenoxyacetic (XIX),

p-bromophenoxyacetic (XX), as well as the phenoxyacetate (XIII) of the second stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 102-103°). The ester of hydroquinonediacetic acid (XXI) was synthesized an an example of an ester of 1,2,5-trimethyl-4-phenyl-4-piperidol and a dibasic acid.



(XXI)

The yield of the esters described decreased considerably when they were isolated by distilling the free base of the ester in vacuum, as in this case partial cleavage of the ester occurred with the formation of the acid and the dehydration product of the alcohol:



According to pharmacological tests, the benzoate (I), phenylacetate (IX), cinnamic ester (X), hydrocinnamic ester (XI) and phenoxyacetate (XIII) of 1,2,5-trimethyl-4-phenyl-4-piperidol have very weak anesthetic (analgesic) activity, but they manifest a strong anesthetic effect many times greater than the effect of novocaine. These compounds, although close in activity to dicaine, are considerably less toxic. Of these esters, the phenoxyacetate of 1,2,5-trimethyl-4-phenyl-4-piperidol (XIII) is particularly interesting as it has a very high anesthetic activity and does not cause irritation of the mucous and cornea membranes, as is observed when the benzoate (I) and phenylacetate (IX) of this piperidol are applied. These negative characteristics are particularly strong in esters of cinnamic and hydrocinnamic acids (X) and (XI).

Thus, the introduction of aromatic radicals into the acyl radical of esters of 1,2,5-trimethyl-4-phenyl-4-piperidol considerably changes the character of the physiological effect of these preparations, and analgesic materials are changed into anesthetic ones. The results of the pharmacological tests of the preparations synthesized by us will be described in more detail in a special report.

EXPERIMENTAL

In all the esterifications we used the high melting γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol with m.p. 107-108°, the preparation of which was described previously [2]. The phenoxyacetate of the β-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol with m.p. 102-103° was also prepared.

The benzoate of 1,2,5-trimethyl-4-phenyl-4-piperidol (I). a) 5 g of 1,2,5-trimethyl-4-phenyl-4-piperidol and 7 ml of benzoyl chloride in 20 ml of benzene was heated for 5 hours at the boiling point of the benzene. The precipitate formed was filtered off, washed several times with benzene and dried in a desiccator. We obtained 5.1 g of the hydrochloride of 1,2,5-trimethyl-4-phenyl-4-piperidyl benzoate (I), which melted at 172-173° after recrystallization from acetone.

Found %: N 3.72, 3.74, 3.86; Cl 9.61. $C_{21}H_{26}O_2NCl$. Calculated %: N 3.89; Cl 9.87.

b) the lithium alcoholate of 1,2,5-trimethyl-4-phenyl-4-piperidol* was prepared from 3.5 g of metallic lithium, 48 g of bromobenzene and 30.g of freshly distilled 1,2,5-trimethyl-4-piperidone in 150 ml of absolute ether. 40 g of of freshly distilled benzoyl chloride was added with vigorous stirring over a period of 2.5 hours to the lithium alcoholate obtained. The following day the reaction mixture was heated with vigorous stirring at the boiling point of the ether for 5 hours and then treated with water (40 ml) while it was cooled and carefully acidified to congo red with 15% hydrochloric acid. The aqueous layer was partially evaporated in vacuum, when a heavy oil separated out and this soon crystallized. The hydrochloride of 1,2,5-trimethyl-4-phenyl-4-piperidyl benzoate (I) formed (43 g) was filtered off and recrystallized from absolute alcohol. The colorless crystals of the hydrochloride, which were difficultly soluble in water, melted at 172-173° and did not depress the melting point of the previous sample.

The residual aqueous layer from the separation of the hydrochloride was treated with soda and extracted with ether and the extract was distilled in vacuum to give two fractions: 1st-b.p. 127-141 at 2.5 mm, 1.3 g; 2nd-b.p. 141-165° at 2.5 mm, 14.4 g. There was 15 g of tarry residue after the distillation. From the 1st fraction we isolated 1 g of the high melting γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol with m.p. 106-107°, which did not depress the melting point of an authentic sample; the 2nd fraction was a mixture of 1,2,5-trimethyl-4-phenyl-4-piperidol and its benzoate; picrates were isolated from it corresponding to the piperidol and the ester. Treatment of the benzoate hydrochloride in aqueous alcohol with ammonia gave the free base of 1,2,5-trimethyl-4-phenyl-4-piperidyl benzoate (I) as colorless crystals with m.p. 111.5-112° (after 2 recrystallizations from benzene).

Found %: N 4.53. $C_{21}H_{25}O_2N$. Calculated %: N 4.33.

Hydrolysis of 1,2,5-trimethyl-4-phenyl-4-piperidyl benzoate with 10% alcoholic caustic potash gave the high melting isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol with m.p. 107°.

The hydrobromide of 1,2,5-trimethyl-4-phenyl-4-piperidyl benzoate melted at 197-198° (from alcohol). The picrate of 1,2,5-trimethyl-4-phenyl-4-piperidyl benzoate, prepared from the free base, melted at 221-221.5° after recrystallization from a large volume of alcohol.

The p-methylbenzoate of 1,2,5-trimethyl-4-phenyl-4-piperidol (II). A mixture of 8.5 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 8.5 ml of benzene, 0.2 g of magnesium and 12.3 g of p-methylbenzoyl chloride (b.p. 90-92° at 8 mm) was heated at 70-75°. After 4 hours heating, crystals began to be deposited from the solution and after 7 hours, crystals were deposited through the whole volume. The precipitate was filtered off, carefully washed with benzene and twice recrystallized from acetone. We obtained 5.0 g of the hydrochloride of 1,2,5-trimethyl-4-phenyl-4-piperidyl p-methylbenzoate (II) as colorless crystals with m.p. 224-225.5°.

Found %: N 3.84, 3.80. $C_{22}H_{24}O_2NCl$. Calculated %: N 3.79.

The p-chlorobenzoate of 1,2,5-trimethyl-4-phenyl-4-piperidol (III). After heating a mixture of 19.4 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 25 ml of benzene, 43 g of p-chlorobenzoyl chloride (b.p. 104° at 11.5 mm) and 0.35 g of magnesium at 70-80° for 7 hours, we obtained 20 g of a crystalline precipitate, which was recrystallized from acetone to give the hydrochloride of (III) with m.p. 214-215°. The yield was 10.4 g.

Found %: N 3.72, 3.93. $C_{21}H_{25}O_2NCl_2$. Calculated %: N 3.56.

The free base (III) was colorless crystals with m.p. 117.5-118.5 (from benzine).

Found %: N 4.13, 3.91. $C_{21}H_{24}O_2NCl$. Calculated %: N 3.91.

The p-bromobenzoate of 1,2,5-trimethyl-4-phenyl-4-piperidol (IV). In the reaction we used 11.5 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 22.7 g of p-bromobenzoyl chloride (b.p. 105-107° at 6 mm), 11.5 ml of benzene and 0.2 g of magnesium. The mixture was heated at 70-75° for 3 hours, after which it was left till the following day. The precipitate was filtered off and twice recrystallized from acetone. We obtained 9.9 g of the hydrochloride of (IV) with m.p. 213-215°.

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* The preparation of the lithium alcoholate of the piperidol was described in the previous report.

Found %: N 3.21, 3.26. $C_{21}H_{24}O_2BrCl$. Calculated %: N 3.30.

The o-methoxybenzoate of 1,2,5-trimethyl-4-phenyl-4-piperidol (V). In the reaction we used 10 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 16.3 g of o-methoxybenzoyl chloride (b.p. 122-123° at 10 mm), 0.2 g of magnesium and 10 ml of benzene. The mixture was heated at 80-90° for 10 hours. The benzene was distilled from the dark red, viscous liquid in vacuum and the residue was dissolved in 15 ml of water. To separate the neutral products, the aqueous solution was washed twice with ether and then treated with soda in the presence of a fresh portion of ether. After drying with sodium sulfate and distilling off the ether, the reaction products were distilled in vacuum. We obtained fractions: 1st-88-94° at 2 mm, 1.8 g; 2nd-100-150° at 2 mm, 0.35 g; 3rd-185-188° at 2 mm, 3.7 g.

Dilution of the 3rd fraction with benzine (b.p. 80-100°) precipitated colorless crystals, which were filtered off and recrystallized from benzine. We obtained 0.5 g of (V) with m.p. 77-79°.

Found %: N 4.13, 3.84. $C_{22}H_{27}O_3N$. Calculated %: N 3.96.

The hydrochloride of (V) was prepared by passing hydrogen chloride into an ether solution of the base. The colorless crystals had m.p. 134-137.5° (after two recrystallizations from acetone).

Found %: N 3.67, 3.48. $C_{22}H_{28}O_3NCl$. Calculated %: N 3.59.

The p-methoxybenzoate of 1,2,5-trimethyl-4-phenyl-piperidol (VI). A solution of 10.6 g of 1,2,5-trimethyl-4-phenyl-4-piperidol and 17 g of p-methoxybenzoyl chloride (b.p. 120-121° at 9 mm) in 10.6 ml of benzene was heated in the presence of 0.25 g of magnesium at 70-75° for 10 hours. Crystallization began only on standing the reaction mixture at room temperature (a day). The precipitated crystalline hydrochloride of (VI) melted at 212.5-213.5° after two recrystallizations from acetone. The yield was 8.4 g.

Found %: N 3.84, 3.80. $C_{22}H_{28}O_3NCl$. Calculated %: N 3.59.

The free base (VI) was prepared from its hydrochloride by treating the aqueous solution with ammonia. The colorless crystals had m.p. 97-98° (from benzine).

Found %: N 4.28, 3.98. $C_{22}H_{27}O_3N$. Calculated %: N 3.96.

The p-nitrobenzoate of 1,2,5-trimethyl-4-phenyl-4-piperidol (VII). The reaction mixture, composed of 10 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 19.5 g of p-nitrobenzoyl chloride, 0.4 g of magnesium turnings and 40 ml of benzene, was heated for 10 hours at 90-95° with continuous stirring. Thirty minutes from the beginning of the reaction, a voluminous fine granular precipitate came down. On the following day the colorless crystalline hydrochloride of (VII) (14 g) was filtered off, washed with benzene and recrystallized from anhydrous alcohol, after which it melted at 201-201.5°. The free base of the p-nitrobenzoate (VII) was prepared by treating an aqueous solution of the hydrochloride with soda and extracting with ether and was a crystalline substance with m.p. 146-147° (from benzine).

Found %: N 7.88, 7.86. $C_{21}H_{24}O_4N_2$. Calculated %: N 7.61.

The p-aminobenzoate of 1,2,5-trimethyl-4-phenyl-4-piperidol (VIII). A solution of 9 g of stannous chloride in 10 ml of alcohol and 10 ml of concentrated hydrochloric acid was gradually added to a solution of 2 g of the hydrochloride of 1,2,5-trimethyl-4-phenyl-4-piperidyl p-nitrobenzoate (m.p. 201-201.5°) in 30 ml of ethyl alcohol, heated to 50°. The mixture was boiled for 5 hours. The alcohol was distilled off under reduced pressure. The residue was washed with ether, dissolved in water and treated with soda and the oil formed was extracted with ether. After drying the ether solution and distilling off the ether, a crystalline residue remained, which was recrystallized from benzene. We obtained 0.9 g of (VIII) as colorless crystals with m.p. 91-92°.

Found %: N 8.52, 8.55. $C_{21}H_{26}O_2N_2$. Calculated %: N 8.28.

The phenylacetate of 1,2,5-trimethyl-4-phenyl-4-piperidol (IX). A solution of 9 g of 1,2,5-trimethyl-4-phenyl-4-piperidol and 10 ml of phenylacetyl chloride (b.p. 105° at 22 mm) in 16 ml of dry benzene was boiled for 6 hours in the presence of 0.3 g of metallic magnesium. The benzene and the excess phenylacetyl chloride were distilled in vacuum and the dark oil left in the flask was washed three times with ether and then dissolved in 50 ml of water. The aqueous solution was treated with soda in the presence of ether. The ether extract of the free base was separated and dried with baked sodium sulfate. After distilling off the ether, the reaction product was distilled in vacuum. Fractions were obtained: 1st-b.p. 148-163° at 2 mm, 3.5 g; 2nd-b.p. 163-176° at 2mm, 2.8 g. There was a residue of 1.5 g after the distillation. Passing dry hydrogen chloride into an ether solution of the 2nd fraction gave 2.7 g of the hydrochloride of (IX) as colorless crystals, which melted at 204-206° after recrystallization from anhydrous alcohol.

Found %: N 4.14, 4.16. $C_{22}H_{28}O_2NCl$. Calculated %: N 3.75.

The cinnamic ester of 1,2,5-trimethyl-4-phenyl-4-piperidol (X). A mixture of 11 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 21 g of cinnamyl chloride (b.p. 250-253°), 0.4 g of magnesium and 20 ml of benzene was boiled gently and stirred for 5 hours. The benzene and excess acid chloride were washed out with several portions of ether. The crystalline residue, which was difficultly soluble in water, was treated with a saturated solution of soda in the presence of ether. Dry hydrogen chloride was passed through the ether solution of the base, after it had been dried with sodium sulfate. We obtained 18 g of the hydrochloride of (X), which melted at 222-224° after recrystallization from acetone.

Found %: N 3.86, 3.86. $C_{23}H_{28}O_2NCl$. Calculated %: N 3.61.

The hydrocinnamic ester of 1,2,5-trimethyl-4-phenyl-4-piperidol (XI). 5.5 g of the hydrochloride of (X)(m.p. 222-224°) dissolved in 100 ml of alcohol, was hydrogenated over a Raney nickel catalyst. It took up 330 ml of hydrogen. After separating off from the catalyst, distilling off the solvent and recrystallizing from acetone, we obtained 5 g of the hydrochloride of (XI) as colorless crystals with m.p. 212-214°.

Found %: N 3.44, 3.72. $C_{23}H_{30}O_2NCl$. Calculated %: N 3.61.

The cyclohexanecarboxylic ester of 1,2,5-trimethyl-4-phenyl-4-piperidol (XII). In the reaction we used 13.8 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 18.5 g of cyclohexanecarboxylic acid chloride (b.p. 179-184°), 14 ml of benzene and 0.2 g of magnesium. The reaction mixture was heated for 10 hours at 70-75°. The benzene was distilled off from the dark red liquid in vacuum. The residue was washed with three portions of ether (15 ml each) and dissolved in 20 ml of acetone, to which was added 15 ml of absolute ether. After 4 days there were deposited crystals of the hydrochloride of the ester of cyclohexanecarboxylic acid and 1,2,5-trimethyl-4-phenyl-4-piperidol, which melted at 99.5-102°. The yield was 0.5 g.

Found %: N 3.96, 3.96. $C_{21}H_{32}O_2NCl$. Calculated %: N 3.83.

The phenoxyacetate of 1,2,5-trimethyl-4-phenyl-4-piperidol (XIII). a) 0.4 g of magnesium was added to 29.2 g of the high melting γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 107-108°), dissolved in 30 ml of benzene, and 45.5 g of phenoxyacetyl chloride (b.p. 120° at 10 mm) was gradually run in. The reaction mixture was heated at 60-65° for 8 hours. After 2 hours heating, crystals began to be deposited from the solution. The precipitate was filtered off and washed with 70 ml of benzene on the filter. We obtained 38.9 g of crystals with m.p. 175.5-178°, from which we isolated 24 g of the pure hydrochloride of (XIII) with m.p. 191-192°, after two recrystallizations from acetone.

Found %: N 3.75, 3.39, 3.64. $C_{22}H_{28}O_3NCl$. Calculated %: N 3.59

This compound was prepared in exactly the same way, but without the addition of magnesium. From 10 g of 1,2,5-trimethyl-4-phenyl-4-piperidol and 15.6 g of phenoxyacetyl chloride we obtained 8.3 g of the hydrochloride of (XIII) with m.p. 190-192°.

b) A mixture composed of 5.5 g of the β-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 102-103°), 8.1 g of phenoxyacetyl chloride, 0.1 g of magnesium and 5 ml of benzene was heated for 10 hours at 60-75°. The benzene was evaporated off in vacuum and by the usual method the residue yielded the free base, which was again treated with 3.6 g of phenoxyacetyl chloride in 5 ml of benzene. After distilling off the benzene and recrystallizing the residue from acetone, we obtained 2.5 g of crystals with m.p. 163-168.5°. After heating with activated charcoal and a further recrystallization, the hydrochloride of 1,2,5-trimethyl-4-phenyl-4-piperidyl phenoxyacetate melted at 162-166°.

Found %: N 3.30, 3.40. $C_{22}H_{28}O_3NCl$. Calculated %: N 3.59.

The p-methylphenoxyacetate of 1,2,5-trimethyl-4-phenyl-4-piperidol (XIV). a) A mixture of 20 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 33.8 g of p-methylphenoxyacetyl (b.p. 115-118° at 9 mm), 0.2 g of magnesium and 20 ml of benzene was heated at 60-65° for 8.5 hours. The crystalline precipitate (21.2 g) was twice recrystallized from acetone. We obtained 10.8 g of the hydrochloride of (XIV) with m.p. 190-191°.

Found %: N 3.26, 3.62. $C_{23}H_{30}O_3NCl$. Calculated %: N 3.47.

b) 17.5 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 29.4 g of p-methylphenoxyacetyl chloride, 0.2 g of magnesium and 17 ml of benzene were heated at 90-95° for 10 hours. The benzene was distilled off in vacuum and the residue was dissolved in 20 ml of water. The aqueous solution was twice washed with ether and then treated with soda. The free base liberated was extracted with ether and distilled in vacuum. Fractions were obtained: 1st-b.p. 95-155° at 2.5 mm, 5.1 g; 2nd-b.p. 155-164° at 2.5 mm, 1.35 g; 3rd – b.p. 165-167° at 2mm, 10.5 g; residue (tar)-6.3 g. From the 3rd fraction we obtained a hydrochloride by passing hydrogen chloride into an ether solution of the base. The hydrochloride was deposited as an oil, which could not be crystallized. 1,2,5-trimethyl-4-phenyl-4-piperidyl p-methylphenoxyacetate was isolated from the 3rd fraction as the picrate, which melted at 184-186° after three recrystallizations from alcohol.

Found %: N 9.68, 9.72. $C_{29}H_{32}O_{10}N_4$. Calculated %: N 9.38.

From the ether solution left after the separation of the hydrochloride, we isolated free p-methylphenoxyacetic acid with m.p. 136-137°.

From the 1st fraction (after distilling it a second time in vacuum) we obtained a picrate with m.p. 125-126°, which was identical with the picrate (m.p. 125-126°) of the dehydration product of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol, prepared by the direct dehydration of this piperidol with 70% sulfuric acid.

The o-methylphenoxyacetate of 1,2,5-trimethyl-4-phenyl-4-piperidol (XV). 10 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 17.8 g of o-methylphenoxyacetyl chloride (b.p. 112-113° at 7 mm), 0.1 g of magnesium and 10 ml of benzene were heated for 2 hours and the reaction mixture was left overnight. The precipitate (13.5 g), after washing with benzene and drying, melted at 172-185°. After two recrystallizations from acetone, we obtained the hydrochloride of (XV) with m.p. 194.5-196°.

Found %: N 3.78, 3.51. $C_{23}H_{30}O_3NCl$. Calculated %: N 3.47.

The o-methoxyphenoxyacetate of 1,2,5-trimethyl-4-phenyl-4-piperidol (XVI). We used 7.7 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 14 g of o-methoxyphenoxyacetyl chloride (b.p. 138-150° at 9 mm), 7 ml of benzene and 0.1 g of magnesium. The reaction was carried out as in the experiment above. We obtained 10 g of a crystalline precipitate with m.p. 185.5-188°. After three recrystallizations from acetone we obtained 6.4 g of the hydrochloride of (XVI) with m.p. 199-200.5°.

Found %: N 3.57, 3.67; Cl 8.48, 8.36. $C_{23}H_{30}O_4NCl$. Calculated %: N 3.34; Cl 8.26.

The p-chlorophenoxyacetate of 1,2,5-trimethyl-4-phenyl-4-piperidol (XVII). In the reaction we used 15.5 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 29 g of p-chlorophenoxyacetyl chloride (b.p. 124-126° at 9 mm), 15 ml of benzene and 0.15 g of magnesium. The mixture was heated for 8 hours at 60-65°. We obtained 21.8 g of a precipitate with m.p. 178-184°, from which we obtained 15.7 g of the hydrochloride of (XVII) with m.p. 184.5-186°, after two recrystallizations from acetone.

Found %: N 3.22, 3.31; Cl 8.50, 8.78. $C_{22}H_{27}O_3NCl_2$. Calculated %: N 3.38; Cl 8.50.

In an experiment where the 1,2,5-trimethyl-4-phenyl-4-piperidyl p-chlorophenoxyacetate was isolated by vacuum distillation of the free base, besides the ester (XVII), we obtained the dehydration product of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol and also p-chlorophenoxyacetic acid with m.p. 150-152°.

The o-chlorophenoxyacetate of 1,2,5-trimethyl-4-phenyl-4-piperidol (XVIII). In the reaction we used 11.8 g of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 107-108°), 21.8 g of o-chlorophenoxyacetyl chloride (b.p. 135-137° at 12 mm), 12 ml of benzene and 0.1 g of magnesium. Heating was continued for 7 hours at 60-65°. We obtained 14 g of a precipitate with m.p. 190-192.5°. After two recrystallizations from acetone, we obtained 12.7 g of the hydrochloride of (XVIII) with m.p. 195.5-197.5°.

Found %: N 3.40, 3.65. $C_{22}H_{27}O_3NCl_2$. Calculated %: N 3.38.

The o,p-dichlorophenoxyacetate of 1,2,5-trimethyl-4-phenyl-4-piperidol (XIX). To a solution of 6.3 g of 1,2,5-trimethyl-4-phenyl-4-piperidol in 7 ml of benzene was added 0.05 g of magnesium and 13.7 g of o,p-dichlorophenoxyacetyl chloride (b.p. 141-148° at 7 mm). The addition of the acid chloride was accompanied by a considerable evolution of heat. Heating was continued for 8 hours at 60-63°. We obtained 9.2 g of crystals with m.p. 193-196°. After two recrystallizations from acetone, we obtained 4.4 g of the hydrochloride of (XIX) with m.p. 202-203°.

Found %: N 3.12, 3.04. $C_{22}H_{26}O_3NCl_3$ Calculated %: N 3.05.

The p-bromophenoxyacetate of 1,2,5-trimethyl-4-phenyl-4-piperidol (XX). In the reaction we used 6 g of 1,2,5-trimethyl-4-phenyl-4-piperidol, 14 g of p-bromophenoxyacetyl chloride (b.p. 141-145° at 10 mm), 10 ml of benzene and 0.05 g of magnesium. The mixture was heated for 6 hours at 60-65°. We obtained 4.3 g of a precipitate with m.p. 185-192°, from which we obtained 2.7 g of the hydrochloride of (XX) with m.p. 194-195.5°, after two recrystallizations from acetone.

Found %: N 2.96, 3.07. $C_{22}H_{27}O_3NBrCl$. Calculated %: N 3.05.

The ester of 1,2,5-trimethyl-4-phenyl-4-piperidol and hydroquinonediacetic acid (XXI). A mixture of 16.6 g of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 107-108°), 10 g of the acid chloride of hydroquinonediacetic acid (m.p. 76-78°), 0.15 g of magnesium and 30 ml of benzene was heated for 8 hours at 60-70°. A very thick, dark red mass was formed, which, after distilling off the benzene, dissolving in water (50 ml) and treating with a dilute aqueous solution of ammonia, yielded the free base of the ester of 1,2,5-trimethyl-4-phenyl-4-piperidol and hydroquinonediacetic acid as colorless crystals with m.p. 148-150° (from benzine). The yield was 6.2 g.

Found %: N 4.47, 4.77. $C_{38}H_{48}O_6N_2$. Calculated %: N 4.46.

The hydrochloride of the ester (XXI) was prepared by passing hydrogen chloride into an ether solution of the base and melted at 226-228° (from alcohol).

Found %: N 3.98, 3.91. $C_{38}H_{50}O_6N_2Cl_2$. Calculated %: N 3.99.

SUMMARY

A series of esters of the high melting isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol and aromatic acids (benzoic phenoxyacetic, phenylacetic, cinnamic, hydrocinnamic, p-aminobenzoic, cyclohexanecarboxylic and hydroquinonediacetic) were synthesized for pharmacological testing. Some of the esters obtained are highly

active anesthetics. The introduction of an aromatic radical into the acyl radical of promidol and compounds similar to it, is accompanied by almost complete disappearance of analgesic activity and the appearance of a strong anesthetic effect in a series of cases.

LITERATURE CITED

[1] I. N. Nazarov et al., J. Gen. Chem. 26, 2798 (1956) (T. p. 3117).*

[2] I. N. Nazarov, V. Ya. Raigorodskaya and V. A. Rudenko, Bull. Acad. Sci. USSR, Div. Chem. Sci. 5, 505 (1949).

M. V. Lomonosov Institute of
Fine Chemical Technology, Moscow

Received October 23, 1955

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[*] T. p. = C. B. Translation pagination.

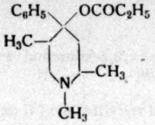
HETEROCYCLIC COMPOUNDS

41. SYNTHETIC ANESTHETICS

VI. ESTERS OF 1,2,5-TRIMETHYL-4-ARYL-4-PIPERIDOLS

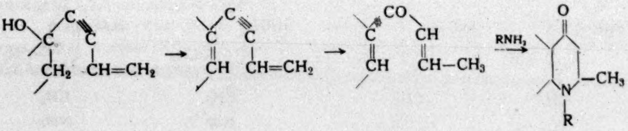
I. N. Nazarov, N. S. Prostakov, Zh. A. Krasnaya and N. N. Mikheeva

Among the esters of 4-phenyl-4-piperidols, compounds were found recently which have extremely high anesthetic activity considerably exceeding that of morphine, and what is especially important, lacking the unpleasant negative properties of the latter (habit formation, high toxicity, side effects on the organism etc). Promedol and isopromedol, which are propionic esters of stereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidols, and were synthesized in our laboratories, are especially interesting anesthetic preparations [1].

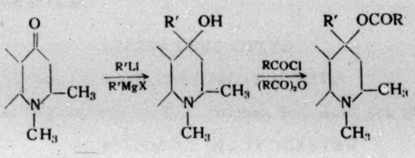


γ-isomer; hydrochloride m.p. 220° (promedol);
β-isomer; hydrochloride m.p. 182° (isopromedol).

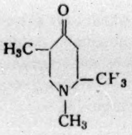
The possibility of obtaining 4-aryl-4-piperidols (the basic intermediate products in the synthesis of the anesthetics) synthetically is determined to a large extent by methods of preparation of 4-piperidones. The synthesis of the latter by the condensation of divinyl ketones with primary amines, developed in our laboratory [2], offers the widest possibilities of obtaining 4-piperidones of various structures.

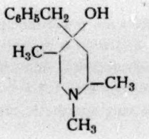


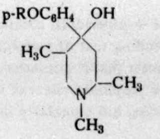
With the aim of finding new anesthetics and for studying systematically the relation between their structure and physiological activity, we synthesized a number of new tertiary 4-piperidols and their esters, by the following general scheme:



The action of benzylmagnesium chloride, anisylmagnesium bromide, phenylmagnesium bromide, p-propoxyphenylmagnesium bromide and p-butoxyphenylmagnesium bromide on 1,2,5-trimethyl-4-piperidone (I) gave 1,2,5-trimethyl-4-benzyl-4-piperidol (II) and 1,2,5-trimethyl-4-p-alkoxyphenyl-4-piperidol (III) in 30-55% yields:


(I)


(II)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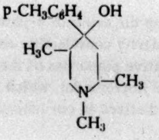
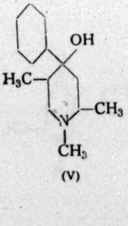

(IV)

$R = CH_3, C_2H_5, C_3H_7, C_4H_9.$

The action of p-tolyllithium on piperidone (I) gave a 55% yield of 1,2,5-trimethyl-4-p-tolyl-4-piperidol (IV), isolated in two stereoisomeric forms with m.p. 113-115° and 136-137°.

The action of cyclohexyllithium [3], cyclohexenyllithium [4] and styryllithium [4] on piperidone (I) gave 1,2,5-trimethyl-4-cyclohexyl-4-piperidol (V), 1,2,5-trimethyl-4-cyclohexenyl-4-piperidol (VI) and 1,2,5-trimethyl-4-styryl-4-piperidol (VII) in approximately 20% yield. Piperidol (VII) split out water when heated with acetyl chloride (120-125°) and was converted into the corresponding tetrahydropyridine derivative (VIII) in 65% yield: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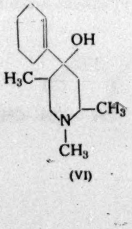
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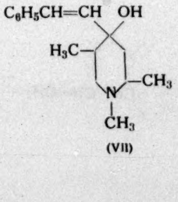
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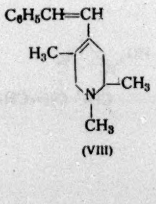
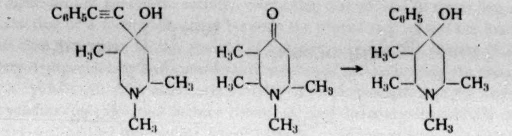

(VIII)

The condensation of phenylacetylene with 1,2,5-trimethyl-4-piperidone (I), by Favorsky's method, gave a 57% yield of 1,2,5-trimethyl-4-phenylethinyl-4-piperidol (IX), isolated in two stereoisomeric forms with m.p. 103-104 and 139-140°.

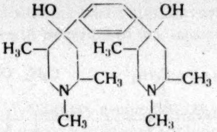
Treating 1,2,5,6-tetramethyl-4-piperidone (X) with phenyllithium gave a 46% yield of 1,2,5,6-tetramethyl-4-phenyl-4-piperidol (XI), also isolated in two stereoisomeric forms with m.p. 99-99.5° and 126-127°.

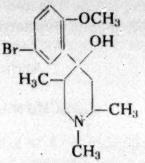

(IX) (X) (XI)

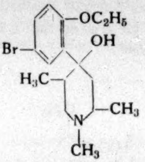
The reaction between piperidone (I) and p-dilithiumbenzene, formed by treating p-dibromobenzene with lithium, proceeded with much more difficulty [5].

p-Di-(1,2,5-trimethyl-4-hydroxy-4-piperidyl)-benzene (XII) was obtained in this reaction in only 2% yield as colorless crystals with m.p. 214-216°.

Treating piperidone (I) with 4-bromo-2-lithiumanisole [6] gave a 20% yield of 1,2,5-trimethyl-4-(2-methoxy-5-bromophenyl)-4-piperidol (XIII) with m.p. 165.5-166°; 1,2, 5-trimethyl-4-(2-ethoxy-5-bromophenyl)-4-piperidol (XIV) with m.p. 122.5-123.5° was obtained in the same way from piperidone (I) and 4-bromo-2-lithiumphenetole:

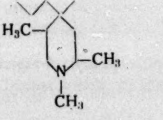

(XII)

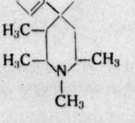

(XIII)


(XIV)

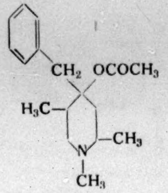
The piperidols obtained are valuable for elucidating the relation between the character of the physiological effect of the esters of these piperidols and their structure.

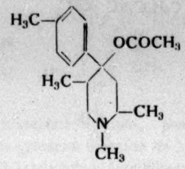
Treatment of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol (V) with acid chlorides gave about 40% yields of the acetate (XV), propionates (XVI) of both stereoisomeric piperidols (V), butyrate (XVII), benzoate (XVIII) and phenoxyacetate (XIX). Acetate (XX), propionate (XXI) and benzoate (XXII) were obtained in the same way by esterifying 1,2,5,6-tetramethyl-4-phenyl-4-piperidol (XI).





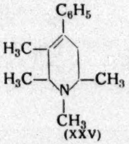
Acetate (XXIII) was obtained in 88% yield by heating 1,2,5-trimethyl-4-benzyl-4-piperidol (II) at 100-120° with acetic anhydride in the presence of hydrogen chloride, while acetate (XXIV) was obtained in 13% yield by treating 1,2,5-trimethyl-4-p-tolyl-4-piperidol (IV) with cyclohexenylacetate (cyclohexanone enolacetate):



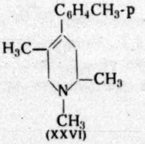


Considerable amounts of dehydration products of the alcohols were formed by raising the temperature to 120-130° (heating sealed ampules) when treating 4-aryl-4-piperidols with acid chlorides. 1,2,5,6-Tetramethyl-4-phenyl-1,2,3,6-tetrahydropyridine (XXV) and 1,2,5-trimethyl-4-p-tolyl-1,2,3,6-tetrahydropyridine (XXVI) were obtained by this method. 1,2,5-trimethyl-4-cyclohexyl-1,2,3,6-tetrahydropyridine (XXVII) was obtained in 72% yield by heating piperidol (V) with propionyl chloride at 60° for 12 hours.

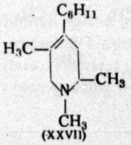
Dehydration of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (XXVIII) (m.p. 107-108°) with 70% sulfuric acid gave a 70% yield of 1,2,5-trimethyl-4-phenyltetrahydropyridine (XXIX) or (XXX), whose picrate melted at 125-126°. Dehydration of the β-isomer (XXVIII) (m.p. 102-103°) under the same conditions gave about 80% yield of another 1,2,5-trimethyl-4-phenyl-tetrahydropyridine (XXIX) or (XXX), whose picrate melted at 156-158°.



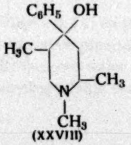
(XXV)



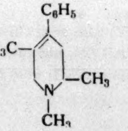
(XXVI)

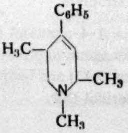


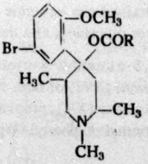
(XXVII)



(XXVIII)







The esters of 1,2,5-trimethyl-4-(2-methoxy-5-bromophenyl)-4-piperidols (XIII) are valuable for elucidating the effect of the halogen and alkoxyl group in the phenyl radical on the anesthetic activity of these compounds.

Acetate (XXXI) was obtained in 49% yield by treating piperidol (XIII) with acetic anhydride, while propionate (XXXII) and benzoate (XXXIII) were obtained by treating the lithium alcoholate of piperidol (XIII) with propionyl and benzoyl chlorides.

The compounds we obtained were tested in the pharmacological laboratory of the All-Union Institute for the Scientific Investigation of Chemical Pharmaceutics. The acetate of 1,2,5-trimethyl-4-benzyl-4-piperidol (XXIII) has neither sedative nor local anesthetic effect. As we had stated earlier [1], the acetate of 1,2,5-trimethyl-4-phenyl-4-piperidol has anesthetic activity, exceeding that of lidol (3 times less active than morphine). Consequently, the introduction of a methylene group between the phenyl radical and the fourth carbon atom of the piperidine ring is in this case the reason for the absence of sedative action in the acetate (XXIII). The analgesic effect of esters of tertiary 4-piperidols is also considerably weakened by exchanging the phenyl radical at the fourth carbon atom for a cyclohexyl. The anesthetic activity of propionate (XVI) of the high melting isomer of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol is three times less than the analgesic activity of the propionate of 1,2,5-trimethyl-4-phenyl-4-piperidol (promedol) described in the previous paper. The propionate (XVI) and the acetate (XV) of the low melting isomer of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol have the same anesthetic activity which is approximately 5 times less than the analgesic activity of promedol. The butyrate (XVII) has absolutely no noticeable analgesic effect.

It is interesting to compare the physiological activity of the acetate (XXXI) and propionate (XXXII) of 1,2,5-trimethyl-4-(2-methoxy-5-bromophenyl)-4-piperidol with the activity of the acetate and propionate of 1,2,5-trimethyl-4-phenyl-4-piperidol. The propionate of 1,2,5-trimethyl-4-phenyl-4-piperidol is among the strongest anesthetics (promedol, isopromedol) while the propionate of 1,2,5-trimethyl-4-(2-methoxy-5-bromophenyl)-4-piperidol (XXXII), as well as acetate (XXXI) have absolutely no noticeable analgesic effect, but they are strong anesthetics, exceeding by many times the activity of novocaine. Consequently, such a change in the character of the physiological effect is determined by the introduction of a substituent (bromine and methoxyl group) into the phenyl radical of promedol and other compounds similar to it.

The benzoate (XXXIII) is approximately 8-9 times more active anesthetically than novocaine, but it produces a sharp irritation when introduced into the conjunctival fold of a rabbit's eye even at 0.25% concentration. Acetate (XXXI) and propionate (XXXII) are so far the only examples of the fact that esters of amino alcohols not only with aromatic but with the lowest aliphatic acids may have strong anesthetic effect. The detailed results of the physiological tests will be published in a separate paper.

EXPERIMENTAL

1,2,5-Trimethyl-4-benzyl-4-piperidol (II). 20 g of 1,2,5-trimethyl-4-piperidone (I) [2] was gradually added with cooling and vigorous stirring to a solution of phenylmagnesium chloride, prepared from 10.4 g of magnesium and 45 g of chlorobenzene in 250 ml of absolute ether. Stirring was continued for 1 hour at room temperature and 3 hours at the boiling point of ether. On cooling, the reaction mixture was treated with dilute hydrochloric acid (until acid to Congo) and then the organic base was isolated from the aqueous layer by treatment with caustic potash and extraction with ether. The residue after distilling off the ether crystallized. We obtained 21.4 g of (II), which melted at 85-87° after recrystallization from benzine (b.p. 80-100°).

Found %: N 6.08, 6.33. $C_{15}H_{23}ON$. Calculated %: N 6.01.

The hydrochloride of the piperidol (II) melted at 212-214° after recrystallization from alcohol.

1,2,5-Trimethyl-4-p-anisyl-4-piperidol (III, R = CH_3). In the reaction we used 11 g of magnesium, 85g of p-bromoanisole, 150 ml of absolute ether and 45 g of (I). The reaction was carried out as described above. Vacuum distillation of the residue from the ether extract of the base gave 26 g of unreacted piperidone (I) (b.p. 43° at 2.5 mm) and 12 g of 1,2,5-trimethyl-4-p-anisyl-4-piperidol (III, R = CH_3) as a viscous liquid, which distilled in the range 135-141° at 2.5 mm and quickly crystallized in the receiver. After two recrystallizations from benzine it melted at 99-100°.

Found %: N 5.80, 5.59. $C_{15}H_{23}O_2N$. Calculated %: N 5.62.

The hydrochloride of 1,2,5-trimethyl-4-p-anisyl-4-piperidol was colorless crystals with m.p. 175-177° (from alcohol).

1,2,5-Trimethyl-4-p-phenetyl-4-piperidol (III, R = C_2H_5). In the reaction we used 7 g of magnesium, 49 g of p-bromophenetole, 17 g of (I) and 300 ml of ether. The reaction was carried out as described above. We obtained 12 g of unreacted piperidone (I) and 7 g of 1,2,5-trimethyl-4-p-phenetyl-4-piperidol (III, R = C_2H_5), which crystallized in the distilling flask after distilling off the piperidone. After recrystallization from benzine, it melted at 118-118.5°.

Found %: N 5.53, 5.78. $C_{16}H_{25}O_2N$. Calculated %: N 5.32.

From the neutral products we isolated 14 g of phenetole (b.p. 168-173°).

1,2,5-Trimethyl-4-p-propoxyphenyl-4-piperidol (III, R = C_3H_7). In the reaction we used 2.83 g of magnesium, 25 g of p-promopropoxybenzene, 200 ml of absolute ether and 8.3 g of (I). We obtained 3.1 g of 1,2,5-trimethyl-4-p-propoxyphenyl-4-piperidol (III, R = C_3H_7) as colorless crystals with m.p. 123-124° (from benzine).

Found %: C 73.57, 73.36 ; H 9.46, 9.43. $C_{17}H_{27}O_2N$. Calculated %: C 73.64 ; H 9.74.

1,2,5-Trimethyl-4-p-butoxyphenyl-4-piperidol (III, R= C_4H_9). In the reaction we used 4.25 g of magnesium, 41.8 g of p-bromobutoxybenzene, 200 ml of absolute ether and 10 g of (I). From the ether extract of the base we obtained 4.7 g of unreacted piperidone (I) and 7 g of 1,2,5-trimethyl-4-p-butoxyphenyl-4-piperidol (III, R = C_4H_9) as colorless needle-like crystals with m.p. 123-124° (after four recrystallizations from benzine).

Found %: N 4.74, 4.55. $C_{18}H_{29}O_2N$. Calculated %: N 4.81.

1,2,5-Trimethyl-4-p-tolyl-4-piperidol (IV). In the reaction we used 3.1 g of metallic lithium, 35 g of p-bromotoluene, 22 g of (I) and 100 ml of absolute ether. The reaction was carried out similarly to the synthesis with lithium described in previous reports. From the ether extract of the base we obtained 13 g of high melting 1,2,5-trimethyl-4-p-tolyl-4-piperidol (IV), which melted at 136-137° after two recrystallizations from benzine.

Found %: N 6.11, 6.41. $C_{15}H_{23}ON$. Calculated %: N 6.01.

By vacuum distillation of the mother liquor, remaining after the isolation of the high melting piperidol (IV), we obtained 3 g of the initial piperidone (I) and 6.8 g of a viscous liquid with b.p.145-148° at 3 mm, which gradually crystallized. By fractional crystallization from benzine we isolated 2.5 g of low melting 1,2,5-trimethyl-4-p-tolyl-4-piperidol with m.p. 113-115°.

Found %: N 5.81, 5.91. $C_{15}H_{23}ON$. Calculated %: N 6.01.

1,2,5-Trimethyl-4-cyclohexyl-4-piperidol (V). To an ether solution of cyclohexyllithium, prepared from 13 g of metallic lithium and 140 g of freshly distilled cyclohexyl chloride (b.p. 140-142°) in 380 ml of absolute ether, 105 g of (I) was added over a period of 2 hours and the addition was carried out at the boiling point of the ether. The material was worked up in the usual way be isolation of the organic bases and distillation in vacuum. We obtained 52 g of unreacted piperidone (I) (b.p. 62-79° at 3 mm) and 26 g of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol (V) as a viscous liquid, which distilled in the range 129-140° at 3 mm. There was 10.8 g of residue after the distillation.

The second fraction crystallized on dilution with benzine. After two recrystallizations, the precipitate from the benzine gave 7.5 g of (V) with m.p. 92-93.5°.

Found %: N 6.33, 6.43. $C_{14}H_{27}ON$. Calculated %: N 6.22.

On standing, the mother liquor remaining after the separation of the piperidol (V) with m.p. 92-93.5, deposited 0.6 g of a second stereoisomeric form of this alcohol, which melted at 125-126.5° after two recrystallizations from benzine.

Found %: N 6.15, 6.48. $C_{14}H_{27}ON$. Calculated %: 6.22.

From the remaining amount we isolated 3.3 g of a mixture of stereoisomeric 1,2,5-trimethyl-4-cyclohexyl-4-piperidols with m.p. 83.5-89°. The residue was an uncrystallizable oil.

1,2,5-Trimethyl-4-cyclohexenyl-4-piperidol (VI). A mixture of 1.8 g of metallic lithium, 70 ml of absolute ether and 15 g of freshly distilled cyclohexenyl chloride was vigorously stirred in an atmosphere of dry nitrogen at the boiling point of the ether for 6 hours. After only one hour, noticeable solution of the lithium began and the solution acquired an intense yellow color. 20 g of piperidone (I) was run into the ether solution of cyclohexenyllithium over a period of 30 minutes with cooling and vigorous stirring. The reaction mixture was stirred for 2 hours at room temperature and for 1 hour at the boiling point of the ether. The organic bases were then isolated by the usual procedure. We obtained 10.2 g of the initial piperidone (I), 2 g of a fraction with b.p. 72-152° and 5 g of 1,2,5-trimethyl-4-cyclohexenyl-4-piperidol (VI) as a viscous liquid, which crystallized on addition of benzine. After recrystallization from benzine, the m.p. was 113-114°.

Found %: N 5.98, 6.17. $C_{14}H_{25}ON$. Calculated %: N 6.27.

1,2,5-Trimethyl-4-styryl-4-piperidol (VII). In the reaction we used 3.86 g of metallic lithium, 55.5 g of bromostyrene, 100 ml of absolute ether and 56 g of (I). The reaction was carried out as described in the previous experiment. We obtained 35.3 g of unreacted piperidone and 21.2 g of 1,2,5-trimethyl-4-styryl-4-piperidol (VII) as a very thick liquid with b.p. 148-150° at 2.5 mm, which set into a glass-like mass. There was 5 g of residue after distillation. We were unable to isolate the piperidol (VII) in a crystalline form. Its picrate melted at 195-198° after two recrystallizations from alcohol.

Found %: N 11.62, 11.74. $C_{22}H_{26}O_8N_4$. Calculated %: N 11.81.

1,2,5-Trimethyl-4-styryl-1,2,3,6-tetrahydropyridine (VIII). 4.2 g of piperidol (VII), 0.1 g of metallic magnesium, 10 ml of benzene and 18 ml of acetyl chloride were heated in sealed ampules for 3 hours at 120-125°. The benzene and acetyl chloride were distilled off under reduced pressure and the residue was dissolved in 25 ml of water, washed with ether to remove neutral products and treated with soda. The organic bases were extracted with ether and distilled in vacuum. We obtained 2.5 g of a mobile liquid with b.p. 133-134° at 2 mm, which was yellow in color and instantaneously decolorized alcoholic permanganate solution. There was 0.7 g of residue after distillation. On standing, the color of the liquid changed and at first it became green and then black. From this fraction we made the iodomethylate of 1,2,5-trimethyl-4-styryl-1,2,3,6-tetrahydropyridine (VIII), which melted at 208-209.5° after three recrystallizations from alcohol.

Found %: N 3.67, 3.69, 3.73. $C_{17}H_{24}NI$. Calculated %: N 3.79.

1,2,5-Trimethyl-4-phenylethinyl-4-piperidol (IX). Into a three-necked flask was placed 17 g of powdered potassium hydroxide, 150 ml of absolute ether and 22 g of piperidone (I). With vigorous stirring and cooling to -5°, 10.5 g of phenylacetylene was run into the reaction mixture over a period of 1 hour, after which stirring was continued for a further 4 hours at room temperature. On the following day the reaction mixture was acidified to Congo with 15% hydrochloric acid. The aqueous solution of the hydrochlorides of the bases was separated, treated with potassium hydroxide and extracted with ether. By distillation of the reaction product in vacuum, we obtained 4.6 g of unreacted piperidone (I) and 17 g of the piperidol (IX) as a very viscous liquid with b.p. 156-158° at 2.5 mm, which set to a glassy mass. There was 1.9 g of residue after distillation. A solution of piperidol (IX) in benzine was heated with activated charcoal and filtered. On cooling there separated a colorless, fine granular crystalline precipitate (13.5 g) of a mixture of stereoisomeric 1,2,5-trimethyl-4-phenylethinyl-4-piperidols, form which we isolated two piperidols by fractional crystallization. The high melting one had m.p. 130-140°.

Found %: N 6.05, 5.91. $C_{16}H_{21}ON$. Calculated %: N 5.76.

The low melting one had m.p. 103-104°.

Found %: N 5.90, 6.01. $C_{16}H_{21}ON$. Calculated %: N 5.76.

1,2,5,6-Tetramethyl-4-phenyl-4-piperidol (XI). Phenylithium was prepared from 34 g of bromobenzene and 2.5 g of metallic lithium in 150 ml of absolute ether. 25 g of freshly distilled piperidone (X) (b.p. 64° at 3.5 mm; n_d^{18} 1.4743 [2]) was gradually added to the phenyllithium, which was cooled to -10° and vigorously stirred. On the following day, after 2 hours heating at the boiling point of the ether, the lithium alcoholate was decomposed with dilute hydrochloric acid (30 ml of concentrated hydrochloric acid in 100 ml of water) with cooling. The ether layer containing the neutral compounds was separated off and the aqueous layer was treated with potassium hydroxide and extracted twice with ether. After drying over sodium sulfate and distilling off the ether, the reaction product was distilled in vacuum. We obtained 8.7 g of unreacted piperidone (X) and 17.5 g of a mixture of stereoisomeric 1,2,5,6-tetramethyl-4-phenyl-4-piperidols (XI) as a viscous pale yellow liquid with b.p. 124-128° at 3 mm. There was a residue of 2.5 g after the distillation.

On cooling and scratching with a rod, the piperidol obtained partially crystallized. After careful washing with benzine on the filter, we obtained 6.5 g of colorless crystals with m.p. 94-105°, from which we isolated two stereoisomeric forms of piperidol (XI) by fractional crystallization from benzine. The low melting form had m.p. 99-99.5°.

Found %: N 6.36, 6.13. $C_{15}H_{23}ON$. Calculated %: N 6.01.

The hydrochloride of the low melting piperidol (XI) melted at 252-253° after two recrystallizations from alcohol. The picrate melted at 162-163° (from alcohol).

The high melting form a piperidol (XI) melted at 126-127°.

Found %: N 5.79, 5.75. $C_{15}H_{23}ON$. Calculated %: N 6.01.

The picrate of the high melting piperidol (XI) melted at 171-172° (from alcohol).

p-Di-(1,2,5-trimethyl-4-hydroxy-4-piperidyl)-benzene (XII). With vigorous stirring a solution of 32.2 g of p-dibromobenzene in 450 ml of petroleum ether was run into a solution of butyllithium, prepared from 74.6 g of butyl bromide and 11.3 g of metallic lithium in 100 ml of petroleum ether, by the usual method. 50 g of (I), dissolved in 50 ml of petroleum ether was added over a period of 6 hours to the p-dilithiumbenzene formed, with cooling in ice water. The next day the reaction mixture was stirred for 10 hours at room temperature and was treated with dilute hydrochloric acid. The aqueous solution of the amine hydrochloride, left after the separation of the ether layer with the neutral products, was treated with soda and then caustic potash until saturated and was extracted several times with ether. After drying with baked sodium sulfate and distilling off the ether, the reaction product was distilled in vacuum; this yielded 18 g of the starting piperidone (I) (b.p. 56° at 3.5 mm), 2.0 g of a fraction, boiling in the range 85-146° at 3 mm, and a residue of 29.5 g of a viscous, dark red, oily liquid, which was dissolved in 25 ml of benzine (b.p. 70-100°). To the solution obtained was added 75 ml of absolute ether. On standing, crystals of (XII) were gradually deposited from the solution, which were filtered off and a new portion of absolute ether was added to the mother liquor again. This operation was repeated 5 times. In this way we isolated 1.1 g of (XII) as colorless crystals with m.p. 214-216°, which were soluble in alcohol, very difficultly soluble in benzine, ether and water and insoluble in acetone.

Found %: C 72.96; H 10.27; N 7.88, 8.02. $C_{22}H_{36}O_2N_2$. Calculated %: C 73.33; H 10.00; N 7.77.

The picrate of (XII) melted at 265° with decomposition (from alcohol).

Found %: N 13.77, 13.80. $C_{34}H_{42}O_{16}N_8$. Calculated %: N 13.69.

We were unable to obtain a crystalline hydrochloride from the mother liquor left after the separation of the glycol (XII).

1,2,5-Trimethyl-4-(2-methoxy-5-bromophenyl)-4-piperidol (XIII). In the reaction we used 3.7 g of metallic lithium, 59.7 g of p-bromoanisole (b.p. 65° at 3.5 mm), 30 g of piperidone (I) and 100 ml of absolute ether. After evaporating off the ether from the ether extract of the base, the residue crystallized. Recrystallization of it from benzine gave 14.5 g of piperidol (XIII) with m.p. 165.5 -166°.

Found %: C 55.00, 54.83; H 6.83, 6.71; N 4.17, 4.37. $C_{15}H_{22}O_2NBr$. Calculated %: C 54.88; H 6.69; N 4.26.

The hydrochloride of (XIII) melted at 233° after recrystallization from alcohol.

The picrate of piperidol (XIII) melted at 188-189.5° after recrystallization from alcohol.

Found %: N 9.86, 9.96. $C_{21}H_{25}O_8N_4Br$. Calculated %: N 10.05.

From the mother liquor, remaining after the isolation of the crystalline piperidol (XIII), we obtained 2.1 g of the starting piperidone (I) and 8 g of a high boiling liquid with b.p. 163-183° at 3.5 mm, whose picrate and hydrochloride were oily materials. From the neutral products we obtained 13 g of anisole and 2.3 g of p-bromoanisole.

1,2,5-Trimethyl-4-(2-ethoxy-5-bromophenyl)-4-piperidol (XIV). In the reaction we used 2.13 g of metallic lithium, 37 g of p-bromophenetole, 17.3 g of piperidone (I) and 150 ml of absolute ether. The reaction was carried out as described above. By distilling the ether extract of the base in vacuum we obtained 5.7 g of unreacted piperidone (I) (b.p. 48-50° at 2.5 mm) and 14.2 g of a viscous liquid with b.p. 155-163° at 2.5 mm, which crystallized on addition of benzine (b.p. 70-100°). There was 1.5 g of a residue after distillation.

After recrystallization from benzine, we obtained piperidol (XIV) as colorless crystals with m.p. 122.5-123.5°.

Found %: C 56.38, 56.28; H 7.16, 7.12. $C_{16}H_{24}O_2NBr$. Calculated %: C 56.14; H 7.01.

From the neutral products we obtained 8.8 g of phenetole and 4 g of p-bromophenetole.

The acetate of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol (XV). 3 g of piperidol (V) (m.p. 92-93.5°), 2.5 g of acetyl chloride and 3.5 ml of dry benzene were boiled for 3 hours. On cooling, a precipitate (2.4 g) of the hydrochloride of piperidol acetate (XV) came out and after recrystallization from acetone it melted at 203-204°.

Found %: N 4.53, 4.44. $C_{16}H_{30}O_2NCl$. Calculated %: N 4.61.

The propionate of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol (XVI). a) To a solution of 5 g of the low melting isomer of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol (V) (m.p. 92-93.5°) in 5 ml of chloroform was added 5 g of propionyl chloride. The solution was kept for two days. The chloroform and excess propionyl chloride were distilled off in vacuum and the crystalline residue was dissolved in dry acetone by heating. On cooling, a colorless precipitate (2.8 g) separated and after drying in a desiccator it melted at 186-189°. By recrystallization from acetone, we obtained the hydrochloride of the propionate of the low melting isomer of piperidol (XVI) with m.p. 194-195.5°.

Found %: N 4.37, 4.49. $C_{17}H_{32}O_2NCl$. Calculated %: N 4.41.

The picrate of 1,2,5-trimethyl-4-cyclohexyl-4-piperidyl propionate, prepared from the free base, melted at 163-164° (from alcohol).

b) 5 g of the low melting isomer of piperidol (V), 4.5 g of propionyl chloride, 0.2 g of metallic magnesium and 5 ml of benzene were boiled on a water bath for 3 hours. On cooling in ice water, we obtained a precipitate (2.5 g) of the hydrochloride of the propionate (XVI), which also melted at 191-193° (from acetone).

c) 2.9 g of propionyl chloride was added to a solution of 3 g of the high melting isomer of piperidol (V) (m.p. 125-126°) in 3 ml of dry benzene. The mixture heated up noticeably. On cooling, over approximately 10 minutes a voluminous, colorless precipitate (3.4 g) separated. After recrystallization from acetone we obtained 2.3 g of the hydrochloride of the propionate of the high melting isomer of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol with m.p. 192-193°. A sample of this mixed with the hydrochloride of the propionate of the low melting isomer of piperidol (V) melted at 171-183°.

Found %: N 4.17, 4.24. $C_{17}H_{32}O_2NCl$. Calculated %: N 4.41.

The butyrate of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol (XVII). 4 g of piperidol (V) (m.p. 92-93.5°), 3.4 g of butyryl chloride and 4 ml of dry benzene were heated for 3 hours at 60-70°. The benzene and excess acid chloride were distilled off in vacuum ; the residual, viscous, dark red oil was dissolved in water (10 ml). The aqueous solution was then treated with soda and the free base was extracted with ether. After drying and distilling off the ether, the reaction product was distilled in vacuum. Fractions were obtained: 1st-b.p. 107-134° at 2 mm, 1.5 g ; 2nd-b.p. 134-149° at 2 mm, 1.9 g. Passing dry hydrogen chloride into an ether solution of the 2nd fraction gave a colorless, crystalline precipitate, which was recrystallized from acetone to yield 1.2 g of the hydrochloride of butyrate (XVII) with m.p. 198.5-199.5°.

Found %: N 4.46, 4.27. $C_{18}H_{34}O_2NCl$. Calculated %: N 4.22.

The benzoate of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol (XVIII). To a solution of 1 g of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol (m.p. 92-93.5°) in 3 ml of benzene was gradually added 1.25 g of benzoyl chloride and 0.01 g of magnesium. The reaction mixture was heated for 14 hours at 70-75°. The benzene was distilled off in vacuum. The residue was washed with three portions of ether and then dissolved in 5 ml of water and treated with dilute ammonia solution. The free base was extracted with ether. On passing hydrogen chloride into the dried ether solution of the base, the hydrochloride was precipitated as a pale yellow oil, which gradually crystallized. After being washed with absolute ether and drying in a desiccator, the hydrochloride of (XVIII) melted at 168-170°.

Found %: N 4.00, 4.07. $C_{21}H_{32}O_2NCl$. Calculated %: N 3.83.

The phenoxyacetate of 1,2,5-trimethyl-4-cyclohexyl-4-piperidol (XIX). In the reaction we used 1 g of piperidol (V) (m.p. 92-93.5°), 2 ml of benzene, 0.05 g of magnesium and 1.5 g of phenoxyacetyl chloride. The reaction was carried out as described above. We obtained 0.6 g of the hydrochloride of the phenoxyacetate (XIX) with m.p. 174-176° (from acetone).

Found %: N 3.78, 3.67. $C_{22}H_{34}O_3NCl$. Calculated %: N 3.53.

The acetate of 1,2,5,6-tetramethyl-4-phenyl-4-piperidol (XX). A solution of 5.4 g of the stereoisomeric 1,2,5,6-tetramethyl-4-phenyl-4-piperidols (XI) (m.p. 94-105°) and 5 ml of acetyl chloride in 20 ml of benzene was heated in the presence of 0.1 g of metallic magnesium for 10 hours with vigorous boiling. The excess acetyl chloride and benzene were distilled off under reduced pressure. To the residue was added 50 ml of absolute ether, the precipitate was filtered off and dissolved in 15 ml of water and the aqueous solution was treated with soda. The oily layer which separated was dissolved in ether, and after drying, was distilled in vacuum. We obtained 4 g of (XX) as a viscous liquid with b.p. 140-142° at 2 mm.

The hydrochloride of the acetate (XX) was prepared by passing hydrogen chloride into an ether solution of the base and in the initial stages of the preparation it was a hygroscopic, crystalline substance. After several recrystallizations from anhydrous alcohol the hydrochloride was obtained as colorless, unhygroscopic crystals with m.p. 199-200°.

Found %: N 4.36, 4.45. $C_{17}H_{26}O_2NCl$. Calculated %: N 4.49.

At the same time we isolated a mixture of hydrochlorides of stereoisomeric 1,2,5,6-tetramethyl-4-phenyl-4-piperidyl acetates with m.p. 154-160°.

Found %: N 4.39, 4.25. $C_{17}H_{26}O_2NCl$. Calculated %: N 4.49.

The propionate of 1,2,5,6-tetramethyl-4-phenyl-4-piperidol (XXI). 5 g of the stereoisomeric 1,2,5,6-tetramethyl-4-phenyl-4-piperidols (m.p. 96-108°) was heated with 10 ml of propionyl chloride in the presence of 0.2 g of magnesium in 12 ml of dry benzene. The reaction product was worked up as described in the previous experiment. We obtained 4.7 g of (XXI) as a viscous liquid with b.p. 148-150° at 2 mm.

Found %: N 4.94, 5.18. $C_{18}H_{27}O_2N$. Calculated %: N 4.84.

The benzoate of 1,2,5,6-tetramethyl-4-phenyl-4-piperidol (XXII). A solution of 9 g of stereoisomeric 1,2,5,6-tetramethyl-4-phenyl-4-piperidols and 11 ml of benzoyl chloride in 16 ml of dry benzene was heated with 0.3 g of metallic magnesium for 8 hours with vigorous boiling. The free base was isolated and the reaction product distilled in vacuum in the usual way. We obtained 9 g of a very viscous liquid with b.p. 165-185° at 2 mm, which changed into a glassy mass on cooling to room temperature. From this we prepared by the usual method a picrate of the benzoate (XXII), which melted at 172-173° after two recrystallizations from anhydrous alcohol.

Found %: N 9.56, 9.42. $C_{28}H_{30}O_9N_4$. Calculated %: N 9.89.

The acetate of 1,2,5-trimethyl-4-benzyl-4-piperidol (XXIII). A solution of 5 g of 1,2,5-trimethyl-4-benzyl-4-piperidol (II) (m.p. 85-87°) in 30 ml of acetic anhydride, saturated with hydrogen chloride, was heated for 3 hours on a boiling water bath and 1.5 hours at 120-130°. The excess acetic anhydride was distilled off in vacuum. The residual oily mass crystallized on washing with ether. We obtained 5.2 g of the hydrochloride of the acetate (XXIII), which melted at 145-146.5° after three recrystallizations from alcohol.

Found %: N 4.38, 4.23. $C_{17}H_{26}O_2NCl$. Calculated %: N 4.49.

The acetate of 1,2,5-trimethyl-4-tolyl-4-piperidol (XXIV). A solution of 3 g of piperidol (IV) (m.p. 136-137°), 6 ml of acetic anhydride and 3 ml of cyclohexenyl acetate, saturated with hydrogen chloride, was heated on Wood's alloy with a continuous increase in the temperature from 100 to 135° over a period of 1.5 hours. At the same time 5 ml of the liquid was distilled off under reduced pressure. The addition of absolute ether to the reaction mixture gave a precipitate, which, after drying in a desiccator, was recrystallized twice from anhydrous alcohol. We obtained 0.5 g of the hydrochloride of the acetate (XXIV) as colorless crystals with m.p. 216.5-217°.

Found %: N 4.49, 4.21. $C_{17}H_{26}O_2NCl$. Calculated %: N 4.49.

An attempt to acetylate 1,2,5-trimethyl-4-p-tolyl-4-piperidol under the same conditions, but without the cyclohexenyl acetate, did not give positive results: from this we obtained the hydrochloride of the starting piperidol with m.p. 196-197°.

Found %: N 5.33, 5.17. $C_{15}H_{23}ONCl$. Calculated %: N 5.22.

1,2,5,6-Tetramethyl-4-phenyl-1,2,3,6-tetrahydropyridine (XXV). A solution of 4 g of piperidol (XI) (m.p. 104-108°) and 10 ml of propionyl chloride in 20 ml of dry benzene was heated with 0.2 g of magnesium in a sealed ampule at 130° for 8 hours. After working up in the usual way by isolating the base and distilling in vacuum, we obtained 3 g of (XXV) as a colorless, mobile liquid with b.p. 99-100° at 2 mm.

The hydrochloride of (XXV) melted at 186-188° after recrystallization from alcohol.

Found %: N 5.88, 6.00. $C_{15}H_{22}NCl$. Calculated %: N 5.60.

1,2,5-Trimethyl-4-p-tolyl-1,2,3,6-tetrahydropyridine (XXVI). 2 g of piperidol (IV) (m.p. 136-138°), 5 ml of propionyl chloride, 12 ml of dry benzene and 0.1 g of metallic magnesium were heated in a sealed ampule at 130-153° for 5 hours. After working up in the usual way and distilling the reaction product in vacuum, we obtained 1.3 g of (XXVI) as a mobile, colorless liquid with b.p. 118-120° at 3 mm.

Found % : N 6.95, 6.87. $C_{15}H_{21}N$. Calculated %: N 6.51.

1,2,5-Trimethyl-4-cyclohexyl-1,2,3,6-tetrahydropyridine (XXVII). A solution of 10 g of (V) (m.p. 92-93.5°) and 9.8 g of propionyl chloride in 10 ml of dry benzene was heated at 50-60° for 12 hours under reflux. The benzene and excess propionyl chloride were distilled off under vacuum ; the residue was dissolved in 20 ml of water and treated with an aqueous solution of ammonia in the presence of ether. After drying and distilling off the ether, the organic bases were distilled in vacuum. Fractions were obtained: 1st -80-84° at 2 mm, 6.6 g ; 2nd-120-135° at 2 mm, 1.6 g. From 1 g of the 1st fraction we obtained a picrate (1.5 g) of (XXVII) with m.p. 111-113° (from alcohol).

Found %: N 13.11, 13.03. $C_{20}H_{28}O_7N_4$. Calculated %: N 12.84.

From 1.6 g of the 2nd fraction we obtained a picrate (2.2 g) of 1,2,5-trimethyl-4-cyclohexyl-4-piperidyl propionate (XVI) with m.p. 163-164° (from alcohol).

Found %: N 11.10, 11.06. $C_{23}H_{34}O_9N_4$. Calculated %: N 10.98.

1,2,5-Trimethyl-4-phenyltetrahydropyridine (XXIX) and (XXX). a) 20 g of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 107-108°), 32 g of 70% sulfuric acid and 4 g of baked copper sulfate were heated for 4 hours on a boiling water bath. The reaction mixture was treated with soda and extracted several times with ether. After drying and distilling in vacuum, we obtained 13.7 g of 1,2,5-trimethyl-4-phenyltetrahydropyridine as a colorless, mobile liquid with b.p. 92-94° at 2.5 mm.

Found %: N 7.14, 7.06. $C_{14}H_{19}N$. Calculated %: N 6.96.

The picrate melted at 125.5-126.5° (from alcohol).

Found %: N 12.95, 12.76. $C_{20}H_{22}O_7N_4$. Calculated %: N 13.02.

The hydrochloride melted at 185-187° (from acetone).

Found %: N 5.98, 6.11. $C_{14}H_{20}NCl$. Calculated %: N 5.89.

Heating 6.4 g of the γ-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol with 20 g of 50% sulfuric acid for 3 hours and working up the reaction product, resulted in 5.6 g (after recrystallization from benzine) of the starting piperidol with m.p. 106-107°.

b) In the reaction we used 2.5 g of the β-isomer of 1,2,5-trimethyl-4-phenyl-4-piperidol (m.p. 101-102°), 4 g of 70% sulfuric acid and 0.5 g of anhydrous copper sulfate. The reaction was carried out as described above. We obtained 1.8 g of 1,2,5-trimethyl-4-phenyltetrahydropyridine as a colorless, mobile liquid with b.p. 81-82° at 2 mm.

The picrate melted at 156-158° (from alcohol).

Found %: N 13.23, 13.22. $C_{20}H_{22}O_7N_4$. Calculated %: N 13.02.

The acetate of 1,2,5-trimethyl-4-(2-methoxy-5-bromophenyl)-4-piperidol (XXXI). A solution of 5 g of 1,2,5-trimethyl-4-(2-methoxy-5-bromophenyl)-4-piperidol (m.p. 165-166°) in 50 ml of freshly distilled acetic anhydride, saturated with hydrogen chloride, was heated for 3 hours on a boiling water bath and then for 5 hours at 130-135°. After distilling off the excess acetic anhydride in vacuum, washing the residue with ether and benzene and recrystallizing it from alcohol, we obtained 3 g of the hydrochloride of (XXXI) with m.p. 217.5-219.5°.

Found %: N 3.84, 3.91. $C_{17}H_{25}O_3NClBr$. Calculated %: N 3.44.

The propionate of 1,2,5-trimethyl-4-(2-methoxy-5-bromophenyl)-4-piperidol (XXXII). The lithium alcoholate of 1,2,5-trimethyl-4-(2-methoxy-5-bromophenyl)-4-piperidol was prepared from 5.9 g of metallic lithium, 103 g of p-bromoanisole and 50 g of 1,2,5-trimethyl-4-piperidone in 150 ml of absolute ether; 75.5 g of propionyl chloride was run in on the following day with vigorous stirring and cooling of the reaction mixture in ice water. The product was worked up in the usual way to isolate the organic bases. By distillation in vacuum, we isolated 28 g of (XXXII) as a viscous liquid with b.p. 157-161° at 2 mm.

The hydrochloride of the propionate (XXXII), in the initial stages of the preparation, was a strongly hygroscopic material, which deliquesced in air. After boiling its alcohol solution with activated charcoal and recrystallizing three times from alcohol, we obtained colorless, unhygroscopic crystals of the hydrochloride of the propionate (XXXII) with m.p. 180-184°.

Found %: N 3.27, 3.36, 3.24. $C_{18}H_{27}O_3NClBr$. Calculated %: N 3.34.

The picrate of the propionate (XXXII) melted at 202-205° after recrystallization from alcohol.

Found %: N 8.95. $C_{24}H_{29}O_9N_4Br$. Calculated %: N 9.13.

On distilling the reaction product in vacuum, besides the propionate (XXXII) we obtained 6 g of a fraction with b.p. 66-129° at 3 mm and 17 g of a substance with b.p. 129-136° at 2.5 mm. There was 11 g of a tarry residue after the distillation.

The benzoate of 1,2,5-trimethyl-4-(2-methoxy- 5-bromophenyl)-4-piperidol (XXXIII). To prepare the lithium alcoholate of 1,2,5-trimethyl-4-(2-methoxy-5-bromophenyl)-4-piperidol we used 5.3 g of metallic lithium, 86 g of p-bromoanisole and 45 g of piperidone (I). 100 g of benzoyl chloride was added dropwise over 5 hours with energetic stirring and cooling of the reaction mixture in ice water. Then the product was treated with 14% hydrochloric acid, the aqueous solution of the amine hydrochloride was saturated with soda, the free base was extracted with ether and the reaction product was distilled in vacuum. This gave a complex mixture of different reaction products. In the range 170-195° 24.5 g of a very viscous liquid distilled over and a second vacuum distillation of this yielded 4 g of 1,2,5-trimethyl-4-(2-methoxy-5-bromophenyl)-4-piperidol (XIII) and 14.5 g of an almost solid residue, which gave, on dissolving in benzine and freezing,, the free base of the benzoate (XXXIII) as colorless crystals with m.p. 138-139.5° (after three recrystallizations from benzine).

Found %: N 3.44, 3.33. $C_{22}H_{26}O_3NBr$. Calculated %: N 3.24.

The hydrochloride of the benzoate (XXXIII) melted at 230-232° (from alcohol).

SUMMARY

A series of new 4-aryl-4-piperidols and their esters were obtained for pharmacological testing.

The introduction of substituents into the phenyl radical of promedol and compounds similar to it, as a rule, sharply impairs the analgesic effect of the preparations, while the analgesic activity completely disappears with the introduction of bromine and methoxyl [ester (XXXII)] but the compound becomes a quite strong anesthetic.

The introduction of a carbon chain between the phenyl and piperidone nucleus of promedol also completely destroys the analgesic activity of the preparation.

The substitution of the phenyl radical in promedol by a cyclohexyl radical decreases the anesthetic effect by 3-5 times.

LITERATURE CITED

[1] I. N. Nazarov et al., J. Gen. Chem. 26, 2798 (1956) (T.p.3131)*.

[2] I. N. Nazarov and V. A. Rudenko, Bull. Acad. Sci., Div. Chem. Sci. 6, 610 (1948).

[3] Gilman and others, J..Am. Chem..Soc., 54, 584 (1935).

[4] Brande, Timmons, J. Am. Chem. Soc., 72, 2000, 2007, 2014 (1950).

[5] Gilman and others, J. Am. Chem. Soc., 62, 2327 (1940).

[6] Wittig, Pockels, Dröge, Ber., 71, 1903 (1938); Wittig, Furman, Ber., 73, 1203 (1940).

M. V. Lomonosov Institute of Fine
Chemical Technology, Moscow

Received October 23, 1955

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* T. p. = C. B. Translation pagination.

HETEROCYCLIC COMPOUNDS

42. SYNTHETIC ANESTHETICS

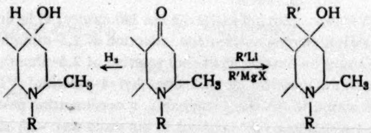
VII. ESTERS OF TERTIARY AND SECONDARY 4-PIPERIDOLS

I. N. Nazarov and N. S. Prostakov

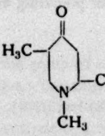
The synthesis of divinyl ketones [1] accomplished in out laboratories opened up a new simple way of obtaining various six-membered heterocyclic γ-ketones and among them γ-piperidones [2] which are important starting materials for the synthesis of physiologically active compounds.

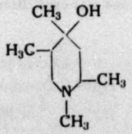
In previous papers we described the synthesis of various esters of 4-aryl-4-piperidols, among which were found some with extremely strong analgesic and anesthetic effects (promedol, isopromedol etc.). For a comparative pharmacological investigation we synthesized various esters of 4-piperidols not containing aromatic substituents in the piperidol nucleus.

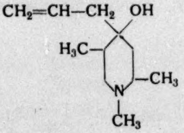
The reaction of 1,2,5-trimethyl-4-piperidone (I) with organomagnesium and organolithium compounds was used to obtain 1,2,5-trimethyl-4-alkyl-4-piperidols, while secondary 4-piperidols were obtained by reducing the corresponding piperidones.

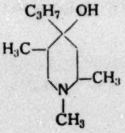


1,2,4,5-Trimethyl-4-piperidol (II) was obtained in low yield (17%) by treating piperidone (I) with methylmagnesium iodide and it was isolated only in one stereoisomeric form. Treatment of piperidone (I) with allylmagnesium chloride gave 1,2,5-trimethyl-4-allyl-4-piperidol (III) in the same low yield and 1,2,5-trimethyl-4-propyl-4-piperidol (IV) was obtained by hydrogenating it.

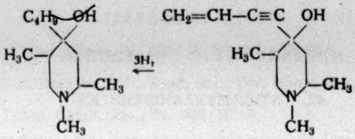




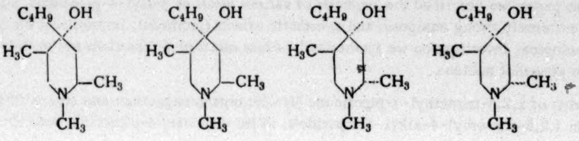




Treatment of piperidone (I) with butyllithium gave 1,2,5-trimethyl-4-butyl-4-piperidol (V) in a 25% yield and it was isolated in only one stereoisomeric form with m.p. 69-69.5°.



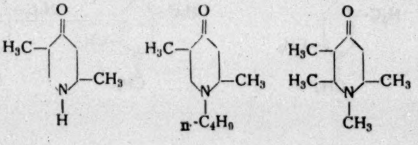
The stereoisomer of butylpiperidol (V) described with m.p. 69-69.5° differs from the two stereoisomeric 1,2,5-trimethyl-4-butyl-4-piperidols (m.p. 91-92° and 111-112°), synthesized earlier in our laboratory [3] by the hydrogenation of the corresponding stereoisomeric 1,2,5-trimethyl-4-vinylethinyl-4-piperidols and, thus, it is the third of the four theoretically possible stereoisomeric forms of this piperidol.

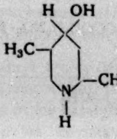


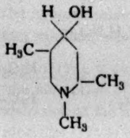
2,5-Dimethyl-4-piperidol (VII) was obtained earlier in our laboratory [4] in three stereoisomeric forms with m.p. 87, 98 and 142° by the catalytic hydrogenation and reduction of 2,5-dimethyl-4-piperidone (VI). We obtained the same piperidol (VII) isomers by heating an alcohol solution of 2,5-dimethyl-4-piperidone with sodium ethylate. This converted about 1/3 of the material into 2,5-dimethyl-4-piperidol (VII) while the remaining 2/3 formed an oil readily soluble in water, which was, presumably, a condensation product of 2,5-dimethyl-4-piperidone. 1-Butyl-2,5-dimethyl-4-piperidone (IX) behaved in the same way with sodium ethylate.

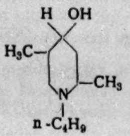
1,2,5-Trimethyl-4-piperidol (VIII) was obtained in 80% yield by the reduction of piperidone (I) with sodium in alcohol. The crystalline piperidol (VIII), described earlier [4], with m.p. 72-73° was isolated from the mixture of stereoisomeric piperidols thus obtained. In the same way, the reduction of piperidol (VIII) gave an 82% yield of a mixture of stereoisomers of 1-butyl-2,5-dimethyl-4-piperidol (X), from which an individual stereoisomer with m.p. 69-71° was isolated. This same piperidol (X) was obtained by treating 1-butyl-2,5-dimethyl-4-piperidone with sodium ethylate.

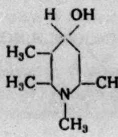
The reduction of 1,2,5,6-tetramethyl-4-piperidone (XI) gave a complex mixture of stereoisomeric 1,2,5,6-tetramethyl-4-piperidols (XII), which was not separated and was used directly for preparing esters.



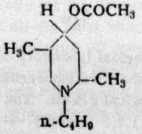


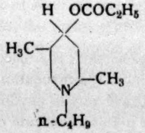


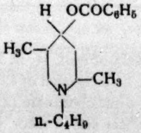




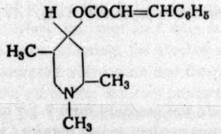
Esterification of piperidol (X) with acetyl, propionyl and benzoyl chlorides gave 40% yields of the corresponding esters-acetate (XIII), propionate (XIV) and benzoate (XV):



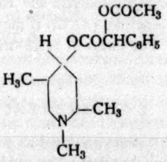




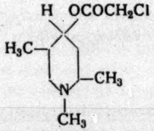
In the same way, the following esters of piperidol (VIII) were obtained: cinnamic (XVI), acetylmandelic (XVII), chloroacetic (XVIII) and β-bromopropionic (XIX):



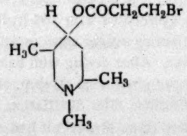
(XVI)



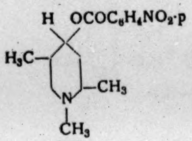
(XVII)



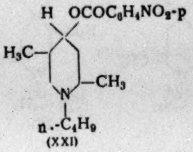
(XVIII)



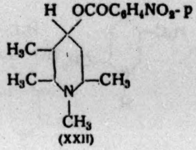
Of the group of esters of secondary 4-piperidols, the benzoic and p-aminobenzoic esters are interesting as anesthetics. Treatment of piperidols (VIII), (X) and (XII) with p-nitrobenzoyl chloride gave the p-nitrobenzoic esters (XX), (XXI) and (XXII) in up to 80% yield. The nitro group in these esters was reduced to the amino group either by catalytic hydrogenation on Raney nickel or with stannous chloride in hydrochloric acid; the p-aminobenzoates (XXIII), (XXIV) and (XXV) were thus obtained almost in quantitative yield:



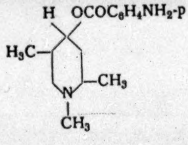
(XX)

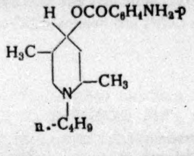


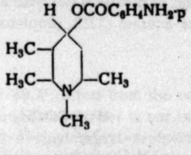
(XXI)



(XXII)







According to the data of Prof. M. D. Mashkovsky's pharmacological laboratory of the All-Union Institute for the Scientific Investigation of Chemical Pharmaceutics, the p-aminobenzoic esters (XXXIII), (XXIV) and (XXV), as well as the p-nitrobenzoate (XX), have various physiological effects. The p-aminobenzoates have a strong anesthetic effect and of them, the p-aminobenzoate of 1,2,5-trimethyl-4-piperidol (XXIII) has an activity close to that of the strongest synthetic anesthetic -dicaine-but with much lower toxicity. The p-aminobenzoate of 1,2,5,6-tetramethyl-4-piperidol (XXV) has a somewhat weaker effect but even it is 4-5 times more active than novocaine. The introduction of an additional methyl group into the piperidine nucleus (see the transition from ester XXIII to XXV) results in a decrease in anesthetic activity as well as toxicity of the compound. The benzoate of 1-butyl-2,5-dimethyl-4-piperidol (XV) has a weak anesthetic effect; it is approximately 10 times weaker than novocaine. As was to be expected, the p-nitrobenzoate of 1,2,5-trimethyl-4-piperidol (XX) has a very weak anesthetic effect, but similar to the corresponding p-aminobenzoate (XXIII) has a slight spasmolytic effect and induces a slight parasympathicolytic and cholinolytic action. An essential drawback of the p-aminobenzoate of 1,2,5-trimethyl-4-piperidol (XXIII) is the fact that aqueous solutions of its hydrochloride gradually lose their activity during storage. The esters of 1,2,5-trimethyl-4-piperidol (XVI), (XVIII) and (XIX) have no interesting physiological effects.

EXPERIMENTAL

1,2,4,5-Tetramethyl-4-piperidol (II). Methylmagnesium iodide was prepared from 7.1 g of magnesium and 37.7 g of methyl iodide in 100 ml of absolute ether. The methylmagnesium iodide obtained was cooled in ice water and stirred while 15 g of piperidone (I) [2] in an equal volume of absolute ether was gradually run in. On the following day the reaction mixture was hydrolyzed with 15% hydrochloric acid (50 ml), the neutral products were extracted with ether and the remaining acidic aqueous solution was treated with potassium hydroxide and extracted several times with ether. After drying with baked sodium sulfate and distilling the product in vacuum, we obtained 11 g of unreacted piperidone (I) (b.p. 58° at 6 mm) and 2.6 g of piperidol (II) with b.p. 70-71° at 3 mm. There was 1.1 g of residue after distillation. The substance gradually crystallized on standing. After recrystallization from benzine (b.p. 70-100°) it had m.p. 87-88°.

Found %: N 9.20, 9.10. $C_9H_{19}ON$. Calculated %: N 8.92.

1,, 2., 5-Trimethyl-4-allyl-4-piperidol (III). In the reaction we used 8.7 g of magnesium, 25 g of allyl chloride, 20 g of piperidone (I) and 100 ml of absolute ether. The reaction was carried out as described above. From the ether extract of the base, after evaporation of the ether, we obtained 2.6 g of crystalline piperidol (III), which melted at 107-108° after recrystallization from benzine.

Found %: N 7.79, 8.07. $C_{11}H_{21}ON$. Calculated %: N 7.65.

Vacuum distillation of the mother liquor, remaining after the separation of the crystalline piperidol (III), yielded 6.5 g of the starting piperidone (I) and 2.5 g of a high boiling fraction (95-115° at 3 mm), which formed a strongly hygroscopic hydrochloride. The hydrochloride of 1,2,5-trimethyl-4-allyl-4-piperidol, prepared by passing dry hydrogen chloride into its ether solution, was colorless crystals with m.p. 122-124° (from alcohol).

1,2,5-Trimethyl-4-propyl-4-piperidol (IV). 2 g of piperidol (III), dissolved in 50 ml of alcohol, was hydrogenated over Raney nickel. After the absorption of the theoretical amount of hydrogen (245 ml, 20°, 765 mm), the separation of the catalyst, evaporation of the alcohol under reduced pressure and recrystallization of the residue from benzine, we obtained piperidol (IV) as colorless crystals with m.p. 86-87°.

Found %: N 7.57, 7.56. $C_{11}H_{23}ON$. Calculated %: N 7.57.

1,2,5-Trimethyl-4-butyl-4-piperidol (V). 75 ml of absolute ether and 2.3 g of finely cut metallic lithium, with all the oxide layer cleaned off, were put in a round bottomed flask fitted with a mechanical stirrer, a reflux condenser, a dropping funnel and an inlet tube for nitrogen. With continuous stirring, 16 g of butyl bromide was gradually run in. The rate of addition was regulated so that the ether boiled all the time. After the introduction of all the butyl bromide, the reaction mixture was stirred for 1.5 hours at room temperature. The residual lithium was separated off from the ether solution of butyllithium by filtration through glass wool in an atmosphere of nitrogen. 10 g of freshly distilled piperidone (I) was gradually added from the dropping funnel to the butyllithium obtained with cooling (from -5 to -10°) and after this, stirring was continued at room temperature for a further 1.5 hours. On the following day 40 ml of dilute hydrochloric acid (1:1) was added with cooling and vigorous stirring, the aqueous layer was separated and treated with potassium hydroxide and the free base was extracted 4 times with ether. After drying with sodium sulfate and distilling the product in vacuum, the ether extract yielded 3.5 g of piperidol (V) with b.p. 85-87° at 2.5 mm, which crystallized in the receiver. After three recrystallizations from petroleum ether, we obtained a colorless crystalline product with m.p. 69-69.5°.

Found %: N 7.16, 7.37. $C_{12}H_{25}ON$. Calculated %: N 7.03.

2,5-Dimethyl-4-piperidol (VII). 7 g of metallic sodium was dissolved in 200 ml of anhydrous alcohol and then 32 g of freshly distilled piperidone (VI) (b.p. 61-63° at 3 mm) [2] was added. The solution, which was completely colorless, was kept for 3 days at room temperature. During this time it acquired an intense red color. After 5 hours refluxing, the alcohol was distilled off, 75 ml of water was added to the residue, the aqueous solution was saturated with potash and the product was extracted several times with ether. After drying and distilling off the ether, the reaction product was distilled in vacuum. We obtained 10.2 g of a viscous, colorless liquid with b.p. 92-110°, which deposited 4.1 g of colorless crystals of piperidol (VII) on adding ether. After careful washing with ether it melted at 134-137°. By crystallization from anhydrous alcohol we isolated a single high melting isomer of 2,5-dimethyl-4-piperidol with m.p. 140.5-141° [4].

Found %: N 10.70, 10.86. $C_7H_{15}ON$. Calculated %: N 10.85.

Its hydrochloride melted at 207-208° after recrystallization from a mixture of alcohol and acetone.

Found %: N 8.60, 8.60. $C_7H_{16}ONCl$. Calculated %: N 8.45.

The picrate of the high melting 2,5-dimethyl-4-piperidol (VII) melted at 181-181.5° (from alcohol).

The uncrystallizable mother liquor remaining after the separation of the high melting isomer of 2,5-dimethyl-4-piperidol was again distilled in vacuum and converted into the hydrochloride, which was recrystallized from anhydrous alcohol to give a hydrochloride with m.p. 218-220°, corresponding to the α-isomer of 2,5-dimethyl-4-piperidol with m.p. 98°.

Found %: N 8.24, 8.29. $C_7H_{16}ONCl$. Calculated %: N 8.45.

On distilling the reaction product in vacuum, besides 10.2 g of a fraction with b.p. 92-110°, we obtained a residue (19.5 g), which was readily soluble in water and hydrochloric acid.

1,2,5-Trimethyl-4-piperidol (VIII). In the reduction we used 30 g of piperidone (I), 350 ml of anhydrous alcohol and 35 g of sodium. The solid reaction mixture was treated with 15% hydrochloric acid (350 ml), the alcohol was distilled off under reduced pressure and the residue was saturated with caustic potash. The organic bases were extracted with ether, dried with baked sodium sulfate and distilled in vacuum. We obtained 23.1 g of piperidol (VIII) with b.p. 78-80° at 4 mm as a colorless, viscous liquid, which deposited 9.0 g of crystals with m.p. 53-64° on long freezing. After three recrystallizations from benzine we isolated one of the stereoisomeric 1,2,5-trimethyl-4-piperidols with m.p. 72-73°.*

Found %: N 9.46, 9.86. $C_8H_{17}ON$. Calculated %: N 9.78.

1-n-Butyl-2-5-dimethyl-4-piperidol (X). a) 43 g of metallic sodium was gradually added to a solution of 52 g of 1-n-butyl-2,5-dimethyl-4-piperidone (IX) in 500 ml of anhydrous alcohol. The base was isolated as in the previous experiment. On distilling the reaction product in vacuum we obtained 43.2 g of piperidol (X) with b.p. 94-95° at 2.5 mm, which crystallized in the receiver and melted at 69-71° after recrystallization from benzene.

Found %: N 7.64, 7.68. $C_{11}H_{23}ON$. Calculated %: N 7.57.

The hydrochloride of piperidol (X) melted at 190-192° after recrystallization from anhydrous alcohol.

Found %: N 6.42, 6.39. $C_{11}H_{24}ONCl$. Calculated %: N 6.32.

From the mother liquor, remaining after the isolation of the crystalline piperidol (X) with m.p. 69-71°, we obtained a mixture of hydrochlorides of stereoisomeric piperidols (X) with m.p. 158-169°.

Found %: Cl 15.70. $C_{11}H_{24}ONCl$. Calculated %: Cl 16.02.

b) 3 g of sodium was dissolved in 55 ml of anhydrous alcohol and then 10 g of piperidone (IX) was run in. The mixture was boiled for 6 hours. The alcohol was distilled off and the residue was dissolved in 35 ml of water and completely saturated with potash. The base was extracted with ether and after drying was distilled in vacuum. We obtained 6 g of piperidol (X) with b.p. 94-95° at 2.5 mm, which crystallized in the receiver. After recrystallization from ether it melted at 69-71°.

The acetate of 1-n-butyl-2,5-dimethyl-4-piperidol (XIII). A solution of 5 g of piperidol (X) (b.p. 94-95° at 2.5 mm) in 20 ml of acetyl chloride, saturated with hydrogen chloride, was boiled for 1.5 hours. After distilling off the excess acetyl chloride in vacuum, there remained a dark, oily mass, which was washed with five portions of ether and then dissolved in alcohol and boiled with activated charcoal. On cooling, very slow crystallization started. We obtained 2.2 g of crystals of the hydrochloride of the piperidyl acetate (XIII) with m.p. 189-192° (from anhydrous alcohol).

Found %: N 5.28, 5.46. $C_{13}H_{26}O_2NCl$. Calculated %: N 5.31.

We isolated a fraction of crystals (0.2 g) with m.p. 117-125°, which was a mixture of hydrochlorides of stereoisomeric 1-n-butyl-2,5-dimethyl-4-piperidyl acetates.

Found %: N 5.08, 5.02. $C_{13}H_{26}O_2NCl$. Calculated %: N 5.31.

The propionate of 1-n-butyl-2,5-dimethyl-4-piperidol (XIV). We used 3 g of piperidol (X) (m.p. 69-71°) and 20 ml of propionyl chloride. The reaction was carried out as described above. The oil remaining after distilling off the acetyl chloride crystallized on prolonged rubbing under a layer of ether. We obtained 3.1 g of the hydrochloride of 1-n-butyl-2,5-dimethyl-4-piperidyl propionate (XIV), which melted at 142-143° after recrystallization from anhydrous alcohol.

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* Its hydrochloride melted at 192-193° [4].

Found %: N 5.15, 5.40. $C_{14}H_{28}O_2NCl$. Calculated %: 5.04.

The benzoate of 1-n-butyl-2,5-dimethyl-4-piperidol (XV). We used 12.5 g of piperidol (X) (b.p. 94-95° at 2.5 mm) and 52 g of benzoyl chloride, saturated with hydrogen chloride. The reaction was carried out as described above. The semicrystalline mass, remaining after distilling off the benzoyl chloride in vacuum, was dissolved in anhydrous alcohol and boiled with activated charcoal. By separating off the charcoal, partially evaporating the solvent and cooling, we isolated 5.8 g of the hydrochloride of 1-n-butyl-2,5-dimethyl-4-piperidyl benzoate (XV) with m.p. 209-211°.

Found %: N 4.55, 4.71; Cl 10.96, 11.05. $C_{18}H_{28}O_2NCl$. Calculated %: N 4.30; Cl 10.90.

The cinnamic ester of 1,2,5-trimethyl-4-piperidol (XVI). 4.5 g of piperidol (VIII) (b.p. 78-80° at 4 mm) and 12.4 g of cinnamyl chloride were heated at 90-100° for 4 hours. The reaction mixture was dissolved in 30 ml of water and washed several times with ether. The residue was treated with soda in the presence of ether. After drying the ether solution of the base and distilling off the ether, the reaction product was distilled in vacuum. We obtained 5 g of the cinnamyl ester (XVI) as a thick liquid with b.p. 157-159° at 2.5 mm, which set to a glassy mass. From this ester we obtained a hydrochloride which melted at 209-211° after recrystallization from alcohol.-

Found %: N 4.73, 4.61. $C_{17}H_{24}O_2NCl$. Calculated %: N 4.52.

The acetylmandelic ester of 1,2,5-trimethyl-4-piperidol (XVII). 8 g of piperidol (VIII), 25 g of acetylmandelyl chloride (b.p. 120-123° at 5 mm), 0.2 g of magnesium and 10 ml of benzene were boiled gently for 10 hours. The benzene distilled off under reduced pressure and the residue was dissolved in water (200 ml) and treated with soda in the presence of ether. By distilling the residue from the ether extract of the base in vacuum, we obtained 9 g of the acetylmandelic ester (XVII) as a very thick liquid with b.p. 191° at 1 mm.

Found %: N 4.75, 4.59. $C_{18}H_{25}O_4N$. Calculated %: N 4.39.

The chloroacetate of 1,2,5-trimethyl-4-piperidol (XVIII). 1.59 g of the hydrochloride of 1,2,5-trimethyl-4-piperidol (m.p. 192-193°) and 10 ml of chloroacetyl chloride were boiled gently for 5 hours. By washing the reaction mixture several times with ether, we obtained 1.7 g of colorless crystals of the hydrochloride 1,2,5-trimethyl-4-piperidyl chloroacetate (XVIII), which melted at 200-202° after recrystallization from acetone.

Found %: N 5.87, 5.53. $C_{10}H_{19}O_2NCl_2$. Calculated %: N 5.47.

The β-bromopropionate of 1,2,5-trimethyl-4-piperidol (XIX). In the reaction we used 1 g of piperidol (VIII) and 2.4 g of β-bromopropionyl chloride. The reaction was carried out as described above, without the isolation of the free base. We obtained 0.8 g of the hydrochloride of 1,2,5-trimethyl-4-piperidyl β-bromopropionate as colorless, needle-like crystals with m.p. 174-175° (from acetone).

Found %: N 4.29, 4.26. $C_{11}H_{21}O_2NBrCl$. Calculated %: N 4.45.

The p-nitrobenzoate of 1,2,5-trimethyl-4-piperidol (XX). 50 g of the mixture of stereoisomeric 1,2,5-trimethyl-4-piperidols (b.p. 76-78° at 3.5 mm) described above and 71.3 g of p-nitrobenzoyl chloride were heated on a boiling water bath for 5 hours. The reaction mixture was washed several times with ether and then dissolved in 50 ml of water. The acidic aqueous solution was twice treated with ether with vigorous shaking in a separating funnel and then with soda in the presence of a fresh portion of ether. After drying over baked sodium sulfate and subsequent distillation of the base, we obtained the following fractions: 1st-b.p. 68-80° at 2.5 mm, 8.5 g; 2nd-b.p. 171-185° at 2.5 mm, 58 g; residue after distillation 3 g.

The 1st fraction completely crystallized in the receiver. After recrystallization from benzine we obtained piperidol (VIII) with m.p. 72-73°. The 2nd fraction was converted into the hydrochloride, which was recrystallized from alcohol to give 18.5 g of the hydrochloride of 1,2,5-trimethyl-4-piperidyl p-nitrobenzoate (XX) with m.p. 204-206°.

Found %: N 8.24, 8.14. $C_{15}H_{21}O_4N_2Cl$. Calculated %: N 8.52.

The remaining fractions of crystals were mixtures of hydrochlorides of the p-nitrobenzoates of the stereoisomeric forms of 1,2,5-trimethyl-4-piperidol.

Found %: N 8.42, 8.67. $C_{15}H_{21}O_4N_2Cl$. Calculated %: N 8.52.

The analysis was carried out on the fraction of the crystalline hydrochloride with m.p. 186-193°.

1,2,5,6-Tetramethyl-4-piperidol (XII). 150 g of metallic sodium was gradually added to a solution of 70 g of piperidone (XI) (b.p. 74-75° at 7 mm) in 1500 ml of anhydrous alcohol. The reaction mixture was heated for 2 hours on a boiling water bath and then acidified with 15% hydrochloric acid (to Congo); the alcohol was distilled off under reduced pressure and the residue was saturated with potassium hydroxide. The bases were extracted with ether and after drying, distilled in vacuum. We obtained 34 g of piperidol (XII) with b.p. 76-78° at 2.5 mm [4].

The p-nitrobenzoate of 1,2,5,6-tetramethyl-4-piperidol (XXII). 16 g of a mixture of stereoisomeric piperidols (XII) and 26.5 g of p-nitrobenzoyl chloride were heated for 2.5 hours on a boiling water bath and 2 hours at 120-125°. After the usual working up we obtained 16.5 g of the p-nitrobenzoate (XII) with b.p. 183-185° at 2.5 mm. There was 13 g of residue after distillation.

The hydrochloride of this ester melted at 200-205° after recrystallization from anhydrous alcohol.

Found %: N 8.28, 8.47. $C_{16}H_{23}O_4N_2Cl$. Calculated %: N 8.17.

The p-nitrobenzoate of 1-n-butyl-2,5-dimethyl-4-piperidol (XXI). We used 2 g of piperidol (X) (m.p 69-71°) and 4 g of p-nitrobenzoyl chloride. The reaction was carried out as described above. We obtained 3.6 g of the hydrochloride of 1-n-butyl-2,5-dimethyl-4-piperidyl p-nitrobenzoate with m.p. 199-200° (from anhydrous alcohol).

Found %: N 7.77, 7.78. $C_{18}H_{27}O_4N_2Cl$. Calculated %: N 7.55.

The p-aminobenzoate of 1,2,5-trimethyl-4-piperidol (XXIII). 4.1 g of the hydrochloride of 1,2,5-trimethyl-4-piperidyl p-nitrobenzoate, dissolved in 100 ml of alcohol, was hydrogenated over Raney nickel. After the absorption of 880 ml of hydrogen (23°, 740 mm), a colorless precipitate of the monohydrochloride of the p-aminobenzoate (XXIII) came out, which was difficultly soluble in alcohol, but dissolved on the addition of 10 ml of water. After separation of the catalyst, evaporation of the alcohol and water under reduced pressure and recrystallization from anhydrous alcohol, we obtained 3 g of the monohydrochloride of 1,2,5-trimethyl-4-piperidyl p-aminobenzoate (XXIII) as colorless crystals with m.p. 260°, which were difficultly soluble in alcohol but readily soluble in water.

Found %: N 9.19, 9.21. $C_{15}H_{23}O_2N_2Cl$. Calculated %: N 9.38.

The p-aminobenzoate of 1,2,5,6-tetramethyl-4-piperidol (XXV). A mixture of 35 g of stannous chloride, 40 ml of hydrochloric acid (d 1.18) and 40 ml of ethyl alcohol was added to a solution of 9 g of the hydrochloride of 1,2,5,6-tetramethyl-4-piperidyl p-nitrobenzoate in 120 ml of ethyl alcohol, heated to 50°. The reaction mixture was heated on a boiling water bath for 5 hours. The alcohol was distilled off under reduced pressure and the residue was dissolved in 30 ml of water and treated with soda in the presence of ether. After drying with baked sodium sulfate, the ether solution of the base was treated with dry hydrogen chloride. The precipitate of the dichloride of 1,2,5,6-tetramethyl-4-piperidyl p-aminobenzoate (XXV) melted at 211-213° (with decomp.) after recrystallization from anhydrous alcohol.

Found %: N 7.71, 7.76. $C_{16}H_{26}O_2N_2Cl_2$. Calculated %: N 8.04.

The p-aminobenzoate of 1-n-butyl-2,5-dimethyl-4-piperidol (XXIV). 0.25 g of the hydrochloride of 1-n-butyl-2,5-dimethyl-4-piperidyl p-nitrobenzoate (m.p. 199-200°), dissolved in 20 ml of ethyl alcohol, was hydrogenated over Raney nickel. After working up in the usual way we obtained 0.2 g of the monohydrochloride of the piperidol p-aminobenzoate (XXIV) as colorless crystals with m.p. 254-255°.

Found %: N 8.46, 8.38. $C_{18}H_{29}O_2N_2Cl$. Calculated %: N 8.22.

SUMMARY

The esterification of 1,2,5-trimethyl-4-piperidol (VIII), 1,2,5,6-tetramethyl-4-piperidol (XII) and 1-n-butyl-2,5-dimethyl-4-piperidol (X) with acid chlorides, for pharmacological tests, gave a series of esters of these alcohols (acetates, propionates, benzoates, p-aminobenzoates, cinnamates etc). The p-aminobenzoic esters of 1,2,5-trimethyl-4-piperidol and 1,2,5,6-tetramethyl-4-piperidol, (XXIII) and (XXV), have high anesthetic activity with a relatively low toxicity.

LITERATURE CITED

[1] I. N. Nazarov et al., Bull. Acad. Sci. USSR, Div. Chem. Sci. 1940, 223, 447, 453, 545; 1941, 211.

[2] I. N. Nazarov and V. A. Rudenko, Bull. Acad. Sci. USSR, Div. Chem. Sci. 6, 610 (1948).

[3] I. N. Nazarov, V. Ya. Raigorodskaya, and V. A. Rudenko, Bull. Acad. Sci. USSR, Div. Chem. Sci. 5, 505 (1949).

[4] I. N. Nazarov, V. A. Rudenko, J. Gen. Chem. 22, 829 (1952) (T. p. 891).*
I. N. Nazarov, D. S. Sokolov, V. N. Rakcheeva, Bull. Acad. Sci. USSR 1954, 80.

Received October 23, 1955

M. V. Lomonosov Institute of Fine Chemical
Technology, Moscow

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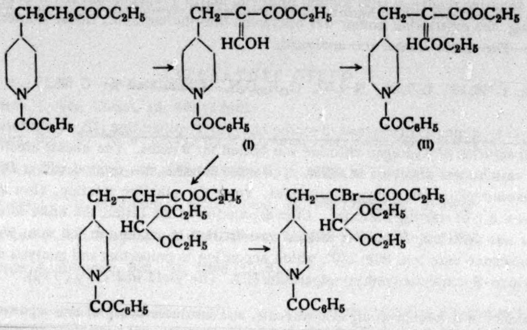
* T. p. = C. B. Translation pagination.

SYNTHESIS OF 1-BENZOYL-4-(β-CARBETHOXY-β-FORMYLETHYL)-PIPERIDINE ACETAL

L. H. Yakhontov and M. V. Rubtsov

During our study of piperidine derivatives we obtained 1-benzoyl-4-(β-carbethoxy-β-hydroxymethyl)-piperidine (I) for the first time. This compound, which is of interest as an intermediate for the synthesis of 4-substituted piperidines and of some quinuclidine derivatives, exists in two geometric forms. Condensation of 1-benzoyl-4-(β-carbethoxyethyl)-piperidine [1] with ethyl formate in the presence of metallic sodium gave an unstable form of (I), which was a thick pale yellow oil.



On standing for several days the oil was converted into colorless crystals with m.p. 114-115° [stable form of (I)]. Neither of the geometric isomers contained an aldehyde group, but were hydroxymethylene derivatives and this was proved by suitable reactions (see the experimental part). The crystalline isomer, in contrast to the unstable isomer, did not react with ferric chloride at the hydroxymethylene group. The crystalline isomer was converted into the unstable liquid isomer by heating to 120° and subsequently cooling. An analogous example of geometric isomerism has been described for hydroxymethylenephenylacetic ester [2].

The conversion of the hydroxymethylene derivative into the acetal of the formyl derivative has been described for hydroxymethylenephenylacetonitrile [3], α-formylhippuric [4] and α-formylphenaceturic [5] esters where the corresponding acetals were obtained by heating the hydroxymethylene derivative with a 1% alcohol solution of hydrogen chloride. 1-Benzoyl-4-(β-ethoxymethylene-β-carbethoxyethyl)-piperidine (II) was formed by applying this same method to 1-benzoyl-4-(β-hydroxymethylene-β-carbethoxyethyl)-piperidine (I). Acetal (III) was obtained simply by treating (I) with orthoformic ester [6]. It was shown that the best results were obtained by using two moles of orthoformic ester per mole of hydroxymethylene derivative. 1-Benzoyl-4-(β-bromo-β-carbethoxy-β-formylethyl)-piperidine acetal (IV) was obtained by treating acetal (III) with bromine in chloroform at room temperature.

EXPERIMENTAL

1-Benzoyl-4-(β-hydroxymethylene-β-carbethoxyethyl)-piperidine (I). A mixture of 14.5 g of 1-benzoyl-4-(β-carbethoxyethyl)-piperidine and 18.5 g of ethyl formate was added with stirring over a period of 1 hour to 1.2 g of metallic sodium in 50 ml of anhydrous ether at −2°. Stirring was continued at this temperature for 6 hours. During this time the sodium reacted. The reaction mixture was treated with 50 ml of water and the unreacted 1-benzoyl-4-(β-carbethoxyethyl)-piperidine was extracted with ether. After distilling off the ether and distilling the residue in vacuum, we recovered 7.0 g of starting material. The aqueous solution was separated, treated with 50 ml of acetic acid and extracted with ether. The ether solution was shaken with fused potash and the ether was distilled off in vacuum. We obtained 8.5 g of a light yellow, oily material. The material was insoluble in water and aqueous solutions of acids and carbonates, was soluble in organic solvents and aqueous solutions of alkalis, gave a positive reaction for a double bond (with potassium permanganate and bromine) and for a hydroxymethylene group (with ferric chloride) and did not give a reaction for an aldehyde (with sodium bisulfite, with Schiff's reagent and with silver oxide). The light yellow oily material was the unstable form of 1-benzoyl-4-(β-carbethoxy-β-hydroxymethyleneethyl)-piperidine; on standing for 5 days in a vacuum desiccator, it was converted into the stable geometric isomer, which was colorless crystals with m.p. 114-115°, poorly soluble in ether (1:400), acetone and water, insoluble in aqueous solutions of acids and carbonates and readily soluble in alcohol, chloroform, benzene, toluene and aqueous solutions of alkalis.

The stable isomer did not give a reaction for a hydroxymethylene group with ferric chloride but gave a positive reaction for a double bond (with potassium permanganate and bromine). The substance did not contain a formyl group (negative reactions with sodium bisulfite, Schiff's reagent and silver oxide). By heating to 120° and subsequent cooling, the crystalline isomer was converted into the unstable, liquid isomer, which had the properites described above. The stable isomer was analyzed.

Found %: C 68.13; H 7.53; N 4.52. $C_{18}H_{23}O_4N$. Calculated %: C 68.17; H 7.25; N 4.41.

1-Benzoyl-4-(β-ethoxymethylene-β-carbethoxyethyl)-piperidine (II). A mixture of 1.8 g of (I) and 18 ml of 1% alcohol solution of hydrogen chloride was boiled for 9 hours. The excess alcohol was distilled off in vacuum and the residue was dissolved in ether. The ether solution was treated with a 5% alkali solution to remove the unreacted hydroxymethylene derivative. From the alkaline solution, after acidification with acetic acid, we isolated 0.6 g of starting material. After separation of the latter, the ether solution was dried with potash, the ether was distilled off and the residue was distilled in vacuum at 0.3 mm. We obtained a thick, colorless, oily substance with b.p. 268-269°, which according to properties and analysis data was 1-benzoyl-4-(β-ethoxymethylene-β-carbethoxyethyl)-piperidine (II). The yield was 1.0 g (77%).

The substance was soluble in organic solvents, and insoluble in water and aqueous solutions of acids and alkalis; it gave positive reactions for a double bond with bromine and potassium permanganate, n_d^{20} 1.5259.

Found %: C 69.64, 69.77; H 8.03, 8.30; N 4.12; OC_2H_5 25.99. $C_{20}H_{27}O_4N$. Calculated %: C 69.56; H 7.82; N 4.06; OC_2H_5 26.08.

The acetal of 1-benzoyl-4-(β-carbethoxy-β-formylethyl)-piperidine (III). A mixture of 12.5 g of (I), 24 ml of anhydrous alcohol, 12 ml of orthoformic ester and 0.03 g of ammonium chloride was boiled for 1.5 hours. Then the reaction mixture was evaporated down in vacuum and the residue dissolved in 25 ml of ether; the unreacted hydroxymethylene derivative was extracted from the ether solution with 5% aqueous potassium hydroxide. The alkaline solution was acidified with acetic acid and extracted with ether. From the ether extract we isolated 5.9 g of starting material. The ether solution, containing the acetal of 1-benzoyl-4-(β-carbethoxy-β-formylethyl)-piperidine, was dried with potash, the ether distilled off in vacuum and the colorless, thick oil, which was obtained, was distilled in vacuum. The b.p. was 298-300° at 0.3 mm. The yield was 6.1 g (72%).

The substance was readily soluble in the usual organic solvents, insoluble in water and aqueous solutions of acids and alkalis and did not give a positive reaction for a double bond with potassium permanganate, n_d^{20}1.5288.

Found %: C 67.34 ; H 8.62 ; N 3.67, 3.72 ; OC_2H_5 33.80. $C_{22}H_{33}O_5N$. Calculated %: C 67.52 ; H 8.44 ; N 3.58 ; OC_2H_5 34.27.

The acetal of 1-benzoyl-4-(β-carbethoxy-β-formyl-β-bromoethyl)-piperidine (IV). A solution of 0.4 g of bromine in 5 ml of anhydrous chloroform was added over a period of 3 hours with stirring at room temperature to a solution of 0.8 g of acetal (III) in 5 ml of dry chloroform. Stirring was continued for a further 5 hours. During this time the solution acquired a light yellow color. The chloroform was distilled off in vacuum, at first at 30° and then at 65°. The residue was dried in a vacuum desiccator over alkali and paraffin. We obtained 0.95 g (99%) of the acetal (IV) as a light yellow, thick oil. The substance was readily soluble in organic solvents and insoluble in water.

Found %: Br 16.98 ; N 2.79. $C_{22}H_{32}O_5NBr$. Calculated %: Br 17.02 ; N 2.98.

SUMMARY

1. 1-Benzoyl-4-(β-carbethoxy-β-hydroxymethyleneethyl)-piperidine was synthesized by condensing 1-benzoyl-4-(β-carbethoxyethyl)-piperidine with ethylformate ; both the geometric isomers of this compound were obtained and their interconversion was carried out.

2. The conditions were found for converting 1-benzoyl-4-(β-carbethoxy-β-hydroxymethylenethyl)-piperidine into the ethoxymethylene compound and into 1-benzoyl-4-(β-carbethoxy-β-formylethyl)-piperidine acetal. 1-Benzoyl-4-(β-carbethoxy-β-formyl-β-bromoethyl)-piperidine acetal was obtained by brominating the latter compound.

LITERATURE CITED

[1]. M. V. Rubtsov, J. Gen. Chem. 16, 461 (1946).

[2] W. Diekmann, Ber., 50, 1375 (1917) ; W. Wislicenus, Lieb. Ann., 312, 34 (1900).

[3] L. T. Strukov, J. Gen. Chem. 22, 1615 (1952) (T. p. 1657).*

[4] A. S. Elina and O. Yu. Magidson, J. Gen. Chem. 21, 780 (1951) (T. p. 861)*.

[5] A. S. Elina and O. Yu. Magidson, J. Gen. Chem. 21, 559 (1951) (T. p. 619)*.

[6] W. Wislicenus, E. Bilhuber, Ber., 51, 1366 (1918).

Received November 5, 1955

S. Ordzhonikidze All-Union Institute for the
Scientific Investigation of Chemical Pharm-
aceutics

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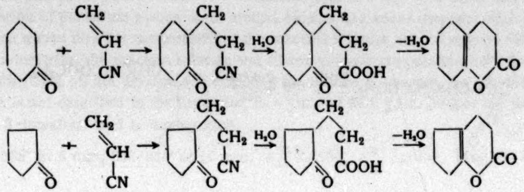
* T. P. = C. B. Translation pagination.

CYANOETHYLATED KETONES IN THE SYNTHESIS OF UNSATURATED δ-LACTONES

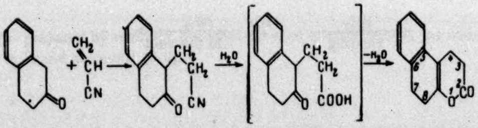
VII. ISOMERIC BENZOTETRAHYDROCOUMARINS*

N. P. Shusherina, R. Ya. Levina and V. I. Zdanovich

As we have reported earlier [1,2], unsaturated δ-lactones with a condensed system of rings may be readily obtained from cyanoethylated cyclic ketones. Thus, $\Delta^{9,10}$-hexahydrocoumarin was obtained from monocyanoethylated cyclohexanone, while 5,6-cyclopentano-3,4-dihydro-α-pyrone was obtained from monocyanoethylated cyclopentanone:



This method was applied in the present work for the synthesis of two new unsaturated δ-lactones with a condensed system of three rings – 5,6-benzo-$\Delta^{9,10}$-tetrahydrocoumarin (III) and 7,8-benzo-$\Delta^{9,10}$-tetrahydrocoumarin (VI). The benzotetrahydrocoumarins, which are similar in structure to santonin, are extremely interesting from the point of view of their possible physiological activity. These two isomeric benzotetrahydrocoumarins were synthesized according to the following scheme:



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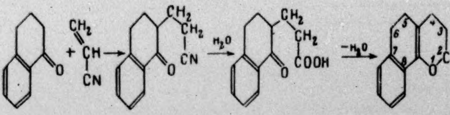
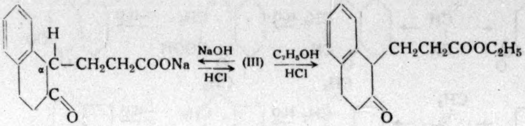
* For report VI see Proc. Acad. Sci. USSR, 109, No. 1 (1956).



As can be seen from the equation given, monocyanoethylated α-and β-tetralones were used as starting materials. Cyanoethylated β-tetralones are not described in the literature. Cyanoethylation of α-tetralone was described by Bruson and Riener [3], who obtained a dicyanoethyl derivative by this reaction; monocyanoethylated α-tetralone was not obtained. Experimentation enabled us to obtain monocyanoethylated β- and α-tetralones. The nitriles – 1-(β-cyanoethyl)-tetralone-2 (I) and 2-(β-cyanoethyl)-tetralone-1 (IV) — were then hydrolyzed.

The hydrolysis of monocyanoethylated β-tetralone was carried out by heating the nitrile with a mixture of concentrated hydrochloric and acetic acids; attempts to hydrolyze with an aqueous solution of caustic potash as well as with concentrated hydrochloric acid were unsuccessful. It is interesting to note that we could not isolate the corresponding δ-keto acid (II) when hydrolyzing monocyanoethylated β-tetralone (I) as its hydrolysis immediately resulted in the unsaturated δ-lactone-5,6-benzo-$\Delta^{9,10}$-tetrahydrocoumarin (III). The lactone, obtained in 80% yield, dissolved completely on heating in an aqueous solution of caustic soda and when the solution was subsequently acidified, the lactone, and not a keto acid, was isolated*. The alcoholysis of lactone (III) gave the ethyl ester of the corresponding keto acid: 1-(β-carbethoxyethyl)-tetralone-2 (VII), which was characterized as the semicarbazone.



According to analysis data, the unsaturated lactam (VIII) 5,6-benzo-$\Delta^{9,10}$ - tetrahydro- α-quinolone) was obtained by the action of an aqueous alcoholic ammonia solution on lactone (III) in the cold; heating the lactone with an aqueous ammonia solution gave the amide of 1-(β-carboxyethyl)-tetralone-2 (IX):

$$\xleftarrow[\text{Heating}]{NH_3} \quad (III) \quad \xrightarrow[\text{In the cold}]{NH_3}$$

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[*] It follows from this that the δ-keto acid (II), corresponding to monocyanoethylated β-tetralone, is incapable of existing and in the moment of formation, in the absence of any kind of dehydrating agent, is converted into the corresponding lactone (III); this is, apparently, due to the great lability of the hydrogen atom in the α-position (activated by the carbonyl group and benzene nucleus) and is related to the readiness of the keto acid to transform into the enol form, required for lactone formation.

Hydrolysis of monocyanoethylated α-tetralone (IV) with a mixture of concentrated hydrochloric and acetic acids gave a keto acid (V) which was converted by heating with acetic anhydride into an unsaturated lactone 7,8-benzo-$\Delta^{9,10}$ --tetrahydrocoumarin (VI). Lactone (VI) was readily hydrolyzed(V) and alcoholyzed (X). According to analysis data, 2-(β-carboxyethyl)-tetralone-1 amide (XI) was obtained by the action of an aqueous ammonia solution on the lactone. Thus, in this case the ammonolysis of the lactone did not result in an unsaturated lactam as was the case in the cold ammonolysis of lactone (III).

$$\xleftarrow[\text{In the cold}]{NH_3} \text{(VI)} \xrightarrow[HCl]{C_2H_5OH}$$

EXPERIMENTAL

Cyanoethylation of β-tetralone•. In a three necked flask, fitted with a stirrer, a thermometer and a reflux condenser, we placed 43 g (0.5 moles) of β-tetralone (b.p. 134-135° at 9 mm), 235 ml of dioxane and 2 ml of a 30% solution of potassium hydroxide in methyl alcohol and added dropwise 26.5 g (0.5 moles) of acrylonitrile at such a rate that the temperature of the reaction mixture did not exceed 40°. At the end of the addition of the acrylonitrile, the reaction mixture was stirred at room temperature for 4 hours and was left overnight. After distilling off the dioxane and distilling the residue in vacuum, we obtained 1-(β-cyanoethyl)-tetralone-2, which is not described in the literature, in a yield of 34.6 g, i.e. 35% of the theoretical and 55% calculated on the β-tetralone used in the reaction.

B. p. 187-188° at 6 mm, 202-204° at 10 mm, n_D^{20} 1.5635, d_4^{20} 1.1367, MR_D 56.96; calc. 56.21. EM_D 0.75••.

Found %: C 77.94, 78.16; H 6.70, 6.66. $C_{13}H_{13}ON$. Calculated %: C 78.36; H 6.66.

Preparation of 5,6-benzo-$\Delta^{9,10}$ --tetrahydrocoumarin (III). A mixture of 26 g of the above prepared nitrile, 96 ml of concentrated hydrochloric acid, 24 ml of water and 40 ml of acetic acid was boiled for 5 hours, diluted with water and extracted with ether. After distilling off the ether and acetic acid and distilling the residue ••• in vacuum, we isolated 16 g of (III); the yield was 88%.

B.p. 192-195° at 8 mm, m.p. 99-100° (from alcohol).

• The β-tetralone was prepared by reducing the ethyl ether of β-naphthol [4] and also by the reduction of β-naphthol with sodium in liquid ammonia [5,6].

•• Exaltation of the molecular refraction (~0.8) is characteristic of compounds of the tetralin series.

••• By recrystallization of the residue (without distilling it) we obtained the same lactone with m.p. 99-100°. Consequently, this disproves the hypothesis that the hydrolysis product of cyanoethylation of β-tetralone is the keto acid (II), which lactonizes on distillation (as described for several keto acids [1]).

Found %: C 77.70, 77.93; H 6.31, 6.25. $C_{13}H_{12}O_2$. Calculated %: C 77.97; H 6.39.

5,6-benzo-$\Delta^{9,10}$ - tetrahydrocoumarin is not described in the literature.

Investigation of the lactone (III). Attempted isolation of a keto acid by alkaline hydrolysis of the lactone. 5 g of the lactone was heated with 10 ml of a 20% aqueous solution of sodium hydroxide until it dissolved completely (20-30 minutes); after acidifying, an oil was isolated, which was the starting lactone (3.5 g); b.p. 193-195° at 8 mm; m.p. 98-99° (from alcohol). A mixed m.p. with the starting lactone was not depressed.

Ammonolysis of the lactone. 5 g of the lactone was dissolved in the cold in 25 ml of a concentrated aqueous solution of ammonia and 10 ml of alcohol; an oil separated, which crystallized on standing; m.p. 176-177° (from ethyl acetate). According to the analysis, we obtained a substance, which was the unsaturated lactam (VIII)-5,6-benzo-$\Delta^{9,10}$ - tetrahydro-α-quinolone (not described in the literature).

Found %: N 7.51, 7.48. $C_{13}H_{13}ON$. Calculated %: N 7.53.

On heating the lactone (3 g) with a concentrated aqueous solution of ammonia and subsequently cooling the solution, a white crystalline substance precipitated, which melted at 189-190° (from ethyl acetate), and according to analysis data, was the amide of 1-(β-carboxyethyl)-tetralone-2 (IX) (not described in the literature).

Found %: N 6.53, 6.71. $C_{13}H_{15}O_2N$. Calculated %: N 6.45.

Alcoholysis of the lactone. A solution of 5 g of the lactone in 50 ml of absolute alcohol was saturated with hydrogen chloride while cooled. The reaction mixture was poured into water and extracted with ether. The 1-(β-carbethoxyethyl)-tetralone-2 (not described in the literature) obtained had the following constants:

B. p. 162.5° at 4 mm, n_D^{20} 1.5394, d_4^{20} 1.1333, MR_D 68.22. $C_{15}H_{18}O_3\bar{F}_3$. Calc. MR_D 67.33. EM_D 0.89.

The semicarbazone of the ester had m.p. 158-159° (from alcohol).

Found %: N 13.90, 13.81. $C_{16}H_{21}O_3N_3$. Calculated %: N 13.86.

Cyanoethylation of α-tetralone*. For the preparation of monocyanoethylated α-tetralone (IV) we used the method described above for the monocyanoethylation of β-tetralone, with the difference that for the same amount of ketone 3 ml of catalyst was used. The yield was 30% of the theoretical and 80% calculated on the α-tetralone which reacted (not described in the literature).

B.p. 204-206° at 8 mm, m.p. 58-60° (from petroleum ether).

Found %: C 78.09, 78.37; H 6.74, 6.66. $C_{13}H_{13}ON$. Calculated %: C 78.37; H 6.66.

Hydrolysis of monocyanoethylated α-tetralone into the keto acid (V). A mixture of 10 g of nitrile, 50 ml of concentrated hydrochloric acid, 10 ml of water and 25 ml of acetic acid was boiled for 8 hours. The precipitated crystals of the keto acid (V) (9.2 g, yield 82.5%) melted at 107° (from aqueous dioxane). According to [9] the m.p. is 107-108°.

Preparation of 7,8-benzo-$\Delta^{9,10}$-tetrahydrocoumarin (VI). A mixture of 9.2 g of the keto acid and 50 ml of acetic anhydride was boiled for 5 hours. After distilling off the acetic anhydride, the residue quickly crystallized. The yield was 83%, m.p. 74.5-75° (from benzine) (not described in the literature).

Found %: C 77.78, 78.02; H 6.11, 6.12. $C_{13}H_{12}O_2$. Calculated %: C 77.98; H 6.39.

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* The α-tetralone was prepared by oxidizing tetralin with atmospheric oxygen [7] with subsequent treatment of the reaction mixture obtained with a solution of chromic acid in acetic acid [8].

Investigation of the lactone (VI). Hydrolysis of the lactone. 0.5 g of the lactone was dissolved in 8 ml of a 20% aqueous solution of potassium hydroxide and boiled for 10 minutes; the cooled solution was acidified with concentrated hydrochloric acid. The hydrolysis product isolated, the keto acid (V) 2-(β-carboxyethyl)-tetralone-1, melted at 106-107° (from aqueous dioxane). A mixed melting point with the authentic keto acid was not depressed.

Alcoholysis of the lactone. A solution of 5.3 g of the lactone in 50 ml of anhydrous alcohol was saturated with hydrogen chloride. After the usual working up we isolated 2-(β-carbethoxyethyl)-tetralone-1 (not described in the literature).

B. p. 182-183° at 6 mm, n_D^{20} 1.5330, d_D^{20} 1.1206, MR_D 68.27. $C_{15}H_{18}O_3F_3$. Calc. MR_D 67.32. EM_D 0.95.

The semicarbazone of 2-(β-carboxyethyl)-tetralone-melted at 157-158° (from alcohol).

Found %: N 13.80 ; 14.05. $C_{16}H_{21}O_3N_3$. Calculated %: N 13.86.

Ammonolysis of lactone. To a mixture of 1 g of the lactone and 2 ml of alcohol was added 8 ml of concentrated aqueous ammonia; considerable evolution of heat occurred and immediately a crystalline material was precipitated with m.p. 147-148° (from alcohol); it did not decolorize bromine water. According to analysis data the material was the amide of 2-(β-carboxyethyl)-tetralone-1 (XI) (not described in the literature).

Found %: N 6.79, 6.76. $C_{13}H_{15}O_2N$. Calculated %: N 6.45.

SUMMARY

1. A method was developed for obtaining new unsaturated δ-lactones with a condensed system of three rings-5,6-benzo-Δ 9,10-tetrahydrocoumarin and 7,8-benzo-Δ 9,10-tetrahydrocoumarin.

2. The structure of the unsaturated δ-lactones obtained was confirmed by their chemical reactions-hydrolysis, alcoholysis, ammonolysis.

3. The preparation of monocyanoethylated derivatives of α-and β-tetralone is described for the first time.

4. Some new derivatives of α-and β-tetralone are described: 1-(β-cyanoethyl)-tetralone-2, 2-(β-cyanoethyl)-tetralone-1, 5,6-benzo-Δ 9,10-tetrahydrocoumarin, 7,8-benzo-Δ 9,10-tetrahydrocoumarin, 1-(β-carbethoxyethyl)-tetralone-2, 2-(β-carbethoxyethyl)-tetralone-1, amides of 1-(β-carboxyethyl)-tetralone-2 and 2-(β-carboxyethyl)-tetralone-1, 5,6,-benzo-Δ 9,10-tetrahydro-α-quinolone.

LITERATURE CITED

[1] R. Ya. Levina, N. P. Shusherina, and T. A. Kaminskaya, Proc. Acad. Sci. USSR 86, 79 (1952).

[2] R. Ya. Levina, N. P. Shusherina, M. Yu. Lurie and V. I. Zdanovich, Herald Moscow State Univ. 1955, No. 10, 123.

[3] H. Bruson, J. Riener, J. Am. Chem. Soc., 64, 2850 (1942).

[4] Syntheses of Organic Preparations, Suppl. 4, p. 454.

[5] A. Birch. J. Chem. Soc., 1944, 430.

[6] J. Barltrop, J. Saxton, J. Chem. Soc., 1952, 1038.

[7] Syntheses of Organic Preparations, Suppl. 3, p. 405.

[8] H. Beyrman, Rec. Trav. chim., 72, 550 (1953).

[9] M. Ansell, D. Hey, J. Chem. Soc., 1950, 2874.

Received October 17, 1955

Moscow State University

BARBITURIC ACIDS

V. METHYLENEMALONIC ESTER IN DIENE SYNTHESIS

SPIROBARBITURIC ACIDS

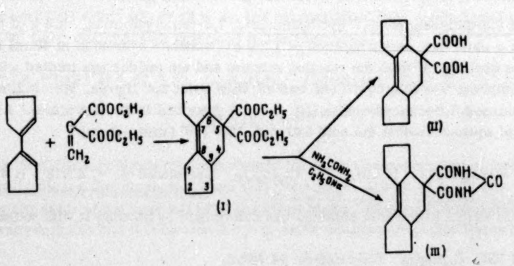
R. Ya. Levina, Yu. S. Shabarov and L. A. Chervoneva

Methylenemalonic ester is an active dienophile [1,2]. It even reacts with those butadiene homologs whose first or fourth atoms of the conjugated system are attached to two alkyl groups [1]; it is known that maleic anhydride does not react with dienes of similar structure.

In our previous paper [1] we described the reaction between methylenemalonic ester with some cyclic and acyclic diene hydrocarbons-cyclopentadiene, cyclohexadiene, piperylene, isoprene and 2,4-dimethylpentadiene-1,3. These reactions make it possible to obtain esters of cyclohexene-gem-dicarboxylic acids, which may be obtained only with difficulty by other means and which could be used in reactions characteristic for malonic esters.

The reaction between methylenemalonic ester and bicyclic dienes-1,1'-dicyclopentenyl and 1,1'-dicyclohexenyl was studied in this work.

1,1'-Dicyclopentenyl and methylenemalonic ester gave the ester of a tricyclic gem-dicarboxylic acid of the cyclopentan-tetrahydroindan series, 5,5-dicarbethoxy-6,7-cyclopentane-Δ 7,8-tetrahydroindan (I), which was characterized by hydrolysis into a dibasic acid (II) and conversion (by treatment with urea) into the corresponding polycyclic spirobarbituric acid (III):



By reaction with methylenemalonic ester, 1,1'-dicyclohexenyl was converted into the ester of a gem-dicarboxylic acid of the dodecanhydrophenanthrene series, 9,9-dicarbethoxy-Δ 4a,5a-dodecanhydrophenanthrene (IV),and the hydrolysis of the latter gave the corresponding monobasic acid (V)*, while reaction with urea gave a polycyclic spirobarbituric acid (VI):

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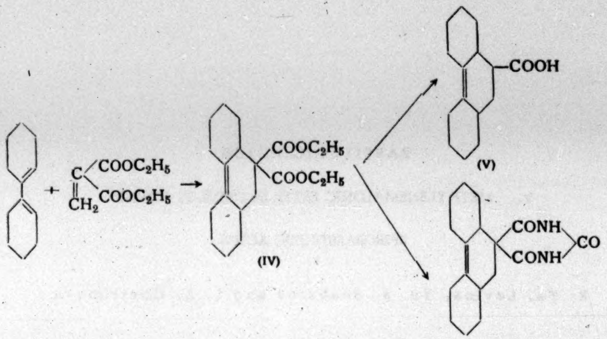
* An attempt has been described to obtain this acid by saponification of the corresponding nitrile (product of acrylonitrile addition to 1,1,'-dicyclohexenyl). However, an amide, stable to hydrolysis and the action of nitric acid, was the main reaction product [3].



EXPERIMENTAL

1,1'-Dicyclopentenyl (b.p. 81-82° at 10 mm, n_d^{20} 1.5237 d_4^{20} 0.9352) was prepared by dehydration of 1,1'-dihydroxydicyclopentyl with acetic anhydride [4] and 1,1'-dicyclohexenyl (b.p. 123-124° at 15 mm, n_d^{20} 1.5319) by dehydration of 1,1'-dihydroxydicyclohexyl with sulfuric acid [5].

Addition of methylenemalonic ester to 1,1'-dicyclopentenyl. 26.2 g of the solid polymer of methylenemalonic ester (m.p. 152-154°), prepared by treating formalin with malonic ester in the presence of diethylamine [6], was depolymerized in a stream of nitrogen by heating to 220-240° in a Wurtz flask; the monomer formed (23 g, 0.13 mole) was distilled off into the reaction flask into which was placed 15 ml of dry benzene. At the end of the depolymerization 10.2 g (0.075 mole) of 1,1'-dicyclopentenyl was put into the flask and the reaction mixture was heated for 6 hours on a boiling water bath with stirring. After distilling off the benzene and distilling the reaction product twice in vacuum, we isolated 12.5 g (54%) of 5,5-dicarbethoxy-6,7-cyclopentano-Δ 7,8-tetrahydroindan (I) (not described in the literature).

B.p. 183-184° (9 mm), n_d^{20} 1.4930, d_4^{20} 1.0924, MR_D 81.41. $C_{18}H_{26}O_4$. Calc. 81.56.

Hydrolysis of 5,5-dicarbethoxy-6,7-cyclopentano-Δ 7,8-tetrahydroindan. 2.5 g of the ester obtained was boiled for 3 hours on a water bath with a solution of 1.2 g of potassium hydroxide in 40 ml of ethyl alcohol. Then the alcohol was distilled off from the reaction mixture and the residue was treated with dilute hydrochloric acid (1:1). The precipitate was filtered off and washed with water and ligroin. We obtained 1.7 g (85%) 5,5-dicarbethoxy-6,7-cyclopentano-Δ 7,8-tetrahydroindan (II) (not described in the literature). After recrystallization from large volumes of aqueous alcohol the acid had m.p. 198-199° (with decomp).

Found %: C 66.85, 67.03; H 7.15, 7.17. $C_{14}H_{18}O_4$. Calculated %: C 67.18; H 7.24.

The molecular weight of the acid obtained was determined by titrating it with sodium hydroxide solution.

Found %: M 251. $C_{14}H_{18}O_4$. Calculated: M 250.3.

Spirobarbituric acid from 5,5-dicarbethoxy-6,7-cyclopentano-Δ 7,8-tetrahydroindan. To sodium alcoholate (14 g of sodium in 25 ml of anhydrous ethyl alcohol) was added 8 g (0.135 mole) of urea and 7.4 g (0.024 mole) of the ester-the addition product of methylenemalonic ester and dicyclopentenyl.

The reaction mixture was heated 6 hours on an oil bath (120-140°) in a flask with a reflux condenser, after which the alcohol was evaporated off and the remaining oil was treated with dilute hydrochloric acid

(1 : 1) until acid. The precipitate was filtered off and washed with petroleum ether (to remove unreacted adduct). We obtained 1.6 g (25%) of spirobarbituric acid (III) (not described in the literature), which melted at 185-186° (decomp) after recrystallization from alcohol.

Found %: C 65.91, 65.82 ; H 6.92, 6.79. $C_{15}H_{18}O_3N_2$. Calculated %: C 65.68 : H 6.61.

Addition of methylenemalonic ester to 1,1'-dicyclohexenyl. The reaction between methylenemalonic ester (22 g, 0.12 mole) and 1,1'-dicyclohexenyl was carried out by the method described above for 1,1'-dicyclopentenyl.

After distilling off the benzene and distilling the residue in vacuum we collected a fraction with b.p. 170-200° (6 mm), which crystallized on standing.

We obtained 15.1 g (74%) of 9,9-dicarbethoxy-Δ 4a,5a-dodecahydrophenanthrene (IV) (not described in the literature).

B.p. 182-184° (6 mm) ; m.p. 66-67° (from alcohol).

Found %: C 71.21, 71.34 ; H 9.11, 9.12. $C_{20}H_{30}O_4$. Calculated %: C 71.82 ; H 9.03.

Hydrolysis of 9,9-dicarbethoxy-Δ 4a,5a-dodecahydrophenanthrene. 4 g of 9,9-dicarbethoxy-Δ 4a,5a-dodecahydrophenanthrene was boiled in a flask with a reflux condenser for 3 hours with a solution of 1.8 g of potassium hydroxide in 60 ml of ethyl alcohol (on a water bath). After distilling off the alcohol, the residue was treated with dilute hydrochloric acid (1 : 1) ; the viscous oil formed was separated from the water ; on rubbing with ligroin it crystallized. The crystals were washed with water and ligroin and recrystallized from large volumes of aqueous alcohol. We obtained 2 g (71%) of the monobasic acid (V) with m.p. 147.5-148.5°.

Found %: M 238 (by titration). $C_{15}H_{22}O_2$. Calculated %: M 234.3.

Reported for 9,9-dicarbethoxy-Δ 4a,5a- dodecahydrophenanthrene [3] : m.p. 148-150°.

Spirobarbituric acid from 9,9-dicarbethoxy-Δ 4a,5a-dodecahydrophenanthrene. To an alcohol solution of sodium alcoholate (1.4 g in 50 ml of anhydrous ethyl alcohol) was added 8 g (0.135 mole) of urea and after it had dissolved, 7.2 g (0.024 mole) of 9,9-dicarbethoxy-Δ 4a,5a-dodecahydrophenanthrene. The reaction mixture was heated on an oil bath in a flask with a reflux condenser for 6 hours at 120-140°, after which the precipitated sodium salt was separated off on a centrifuge and treated with dilute hydrochloric acid (1 : 1) until acid. We obtained spirobarbituric acid (VI) which was dried in air and recrystallized from alcohol (yield 0.5 g, 7.5%). The m.p. of (VI) was 267-268° (with decomp) (not described in the literature).

Found %: C 67.38, 67.18 ; H 7.47, 7.32. $C_{17}H_{22}O_3N_2$. Calculated : C 67.51 ; H 7.33.

SUMMARY

1. It was shown that diene synthesis proceeds readily (in boiling benzene solution) between methylenemalonic ester and bicyclic dienes, dicyclopentenyl and dicyclohexenyl, and leads to the formation of esters of tricyclic gem-dicarboxylic acids which have not been described in the literature-5,5-dicarbethoxy-6,7-cyclopentan-Δ 7,8-tetrahydroindan and 9,9-dicarbethoxy-Δ 4a,5a-dodecahydrophenanthrene (in 54 and 74 % yield).

2. The esters obtained of gem-dicarboxylic acids were converted by treatment with urea (in the presence of sodium ethylate) into the corresponding polycyclic spirobarbituric acids (not described in the literature).

LITERATURE CITED

[1] R. Ya. Levina and N. N. Godovikov, J. Gen. Chem. 25, 986, 2522 (1955) (T. p. 951)*.

[2] G. B. Bachman, H. A. Tanner, J. Org. Ch., 4, 493 (1939).

[3] E. D. Bergmann, H. Davies, R. Pappo, J. Org. Ch., 17, 1331 (1952).

[4] R. Ya. Levina, V. R. Skvarchenko and O. Yu. Okhlobystin, J. Gen. Chem. 25, 1466 (1955) (T. p. 1411).*

[5] I. N. Nazarov, and L. V. Torgov, J. Gen. Chem. 22, 228 (1952) (T. p. 281).*

[6] R. Ya. Levina and N. N. Godovikov, J. Gen. Chem. 24, 1342 (1954).

Received September 17, 1955

Moscow State University

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* T. p. = C. B. Translation pagination.

INVESTIGATIONS IN THE FIELD OF ALKANESULFO ACIDS

XV. CHLORINATION OF ANILIDES OF ALKANESULFO ACIDS

A. G. Kostsova, N. M. Yanova and Z. N. Sushko

The chlorination of alkanesulfoamides has been little studied. However,we had previously shown that N-dichlorosulfoamide was formed by the action of elementary chlorine on an aqueous solution of chloromethanesulfoamide [1]. Later [2] a whole series of N-dichloroamides of alkanesulfo acids were obtained by the same method and, moreover, the bleaching and germicidal properties of these compounds were also demonstrated. From the patent literature it is known that N-chloroamides are also formed by the chlorination of N-alkylamide [3]. Chlorination of N-arylamides of alkanesulfo acids is not described in the literature. Chattaway [4] showed that N-chloroanilides are formed by the action of hypochlorous acid or bleaching powder on a chloroform solution of aromatic sulfo acid anilides in a neutral medium, as in acidic or alkaline media regrouping of N-chloroanilide takes place with the transfer of halogen from nitrogen into the aromatic nucleus and in an acidic medium the regrouping goes mainly into the para-position; in alkali, however, it goes into the ortho-position. N-chloro-2,4-dichloroanilide is formed by chlorinating the anilide with excess bleaching powder in glacial acetic acid.

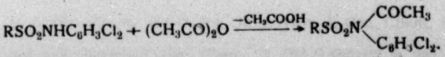
It seemed interesting to study the effect of elementary chlorine on the anilides of various alkanesulfo acids. We used ethane-and butanesulfoanilides for this purpose. The chlorination was carried out under various conditions. Colorless crystalline materials with a characteristic smell were isolated by carrying out the reaction in carbon tetrachloride and cooling it to from 0 to -5° in the presence of ZnO which was the reagent for bonding the HCl produced. Quantitative analysis for N, S and Cl showed that they were dichloro derivatives of the anilide. The properties of these compounds were typical of N-arylamides: they dissolved in dilute alkali from which they were again separated by acidifying, they dissolved readily in organic solvent, but with difficulty in water; they did not give a reaction for active chlorine with KI nor did they have the smell typical of N-chloroamides; they formed sodium salts when treated with metallic sodium in an ether solution; furthermore, the salt was a white amorphous powder in the case of ethanesulfodichloroanilide while it was a sticky, viscous mass in the case of butanesulfodichloroanilide. Both salts were readily decomposed by hydrochloric acid with the formation of the original dichloroanilide and NaCl. N-acetyl derivatives were formed by acetylation of the dichloroanilides with acetic anhydride, although in this case the acetylation occurred under more drastic conditions than with unsubstituted anilides. Methylation of the dichloroanilides proceeded with great difficulty with the formation of viscous, difficultly identifiable products, while at the same time unchlorinated anilides were readily methylated.

It was thus established that when anilides are chlorinated with elementary chlorine in carbon tetrachloride, the hydrogen atom at the nitrogen is not involved and that both chlorine atoms go into the aromatic nucleus. The reaction may be expressed by equation (1):

$$RSO_2NHC_6H_5 + 2Cl_2 + ZnO \rightarrow RSO_2NHC_6H_3Cl_2 + ZnCl_2 + H_2O.$$

The formation reactions of the sodium salt and dichloroanilide N-acetyl derivatives may be expressed by equation (2) and (3):

$$2RSO_2NHC_6H_3Cl_2 + 2Na \xrightarrow{-H_2} 2RSO_2NNaC_6H_3Cl_2,$$

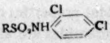


$$RSO_2NHC_6H_3Cl_2 + (CH_3CO)_2O \xrightarrow{-CH_3COOH} RSO_2N\begin{matrix} \diagup COCH_3 \\ \diagdown C_6H_3Cl_2. \end{matrix}$$

The yield of ethanesulfodichloroanilide was up to 95%, that of butanesulfodichloroanilide up to 72%.

The same products were obtained but in much lower yields by carrying out the reactions under the same conditions but without ZnO; thus, for example, 34-35% of ethanesulfodichloroanilide was formed and 8-9% of butanesulfodichloroanilide. Zinc oxide was used by us as a reagent for bonding the HCl produced during the reaction but it is very probable that the zinc chloride, formed by the reaction of the oxide with HCl, plays the part of an active catalyst in this reaction.

It is known from the literature [5], that the sulfoamide group is ortho and para directing. On this basis, we assumed a structural formula for the dichloroanilides obtained by us to be (A):



(A)

We carried out the hydrolysis of these compounds to verify this structure. As a rule, the original product remained unchanged by boiling for several hours at first in a 7-8% and then in a 15% solution of caustic alkali, which indicates the high stability of dichloroanilides to cleavage in an alkaline medium. The hydrolysis was carried out by boiling for several hours with sulfuric acid, diluted 1:1. 2,4-dichloroaniline with m.p. 62° was isolated by adding alkali to the acidic solution in both ethane-and butanesulfodichloroanilide hydrolysis, although the hydrolysis of the latter took longer than that of the former.

Chlorination of the anilides in an alkaline medium resulted in the same dichloroanilide in the case of ethanesulfoanilide, while no pure product could be isolated in the case of butanesulfoanilide although, presumably, butanesulfodichloroanilide was also formed.

EXPERIMENTAL

The starting anilides were prepared by the method which we described earlier [6].

1. Chlorination of ethanesulfoanilide. To 5 g of ethanesulfoanilide, suspended in 35 ml of carbon tetrachloride, was added 2.2 g of ZnO and with cooling to 0 to-5°, a strong stream of chlorine was passed in for 1 hour 15 minutes. The reaction mixture heated up to 8-10°. The ethanesulfoanilide dissolved in the CCl_4. In proportion to the extent of chlorination, the amount of ZnO noticeably decreased. At the end of the chlorination the reaction mixture was left to stand till the next day. White crystals gradually deposited, which were separated off and dried. The yield was 6.5 g (95.5%). After recrystallization from alcohol and water, the m.p. was 67°. The product was readily soluble in alcohol, acetone, ether, benzene and other organic solvents and also in dilute alkali, from which it was again isolated by acidification. It dissolved in water only on boiling. Iodine was not liberated from potassium iodide in an acid medium.

Chlorination of ethanesulfoanilide in carbon tetrachloride with zinc oxide in half the amount given above (1/2 a mole to 1 mole of anilide) showed that the yield of dichloroanilide considerably decreased (to 78.6%) and chlorination of the same amount of anilide in the absence of zinc oxide gave a yield of 35.3% of the dichloroanilide.

Found %: N 5.52; Cl 27.85; S 12.38. $C_8H_9O_2NSCl_2$. Calculated %: N 5.51; Cl 27.96; S 12.59.

2. Chlorination of butanesulfoanilide. 9.5 g of butanesulfoanilide in 35 ml of carbon tetrachloride and in the presence of 3.7 g of zinc oxide was chlorinated for 1.5 hours as in the previous experiment. The yield of product was 9.05 g (72%). It was recrystallized from alcohol and water. The m.p. was 69-70°. The dichloroanilide had a characteristic smell. The solublity was similar to the solubility of the previous product. Chlorination of butanesulfoanilide with half the amount of zinc oxide used in the above experiment gave 31% yield of the dichloroanilide. Chlorination of the same amount of anilide without zinc oxide lowered the yield of dichloroanilide to 8.46%.

Found %: N 4.97; Cl 25.23; S 11.08. $C_{10}H_{13}O_2NSCl_2$. Calculated %: N 4.96; Cl 25.19; S 11.34.

3. Chlorination in an alkaline medium. A strong stream of chlorine was passed for 1.5 hours with stirring into 5 g of ethanesulfoanilide, dissolved in 20 ml of 7.5% alkali solution, cooled to from 0 to -3°. During the chlorination a greyish solid product precipitated from the solution and at the end of the chlorination it was separated off and dissolved in ether; the ether solution was washed with water, separated from the water and dried with calcium chloride. Then the ether was distilled off and the residue crystallized after standing for a day. The yield was 5.9 g (86.7%). After recrystallization from alcohol and water, the product melted at 66-67° and dissolved in organic solvents and dilute alkali, from which it was isolated on acidification. With acetic anhydride it formed an N-acetyl derivative with m.p. 126-127°.

Found %: N 5.58. $C_8H_9O_2NSCl_2$. Calculated %: N 5.51.

On chlorinating butanesulfoanilide in an alkaline medium a very impure product was isolated, which could not be identified.

4. Preparation of the sodium salt of ethanesulfodichloroanilide. 0.091 g of sodium was added in small pieces to a solution of 1 g of ethanesulfodichloroanilide in 10 ml of absolute ether. We observed the copious evolution of bubbles of hydrogen and the gradual formation of a white turbidity. After several hours standing, all the metallic sodium reacted. A white amorphous precipitate formed, which was filtered off and washed with absolute ether. The yield of the salt was 0.9 g (83.3%). The salt was readily soluble in cold water whereupon the solution was accompanied by hydrolysis, the stage of which was determined by titration of the alkali liberated. On treating the salt with hydrochloric acid it decomposed to give the original dichloroanilide.

Found %: N 5.04. $C_8H_8O_2NSCl_2Na$. Calculated %: N 5.07.

5. Preparation of the sodium salt of butanesulfodichloroanilide. We used 1 g of butanesulfodichloroanilide in 10 ml of absolute ether and 0.082 g of metallic sodium. The reaction was carried out as in the previous one. The sodium salt was obtained as a brown mass, deliquescing in air.

Found %: N 4.26. $C_{10}H_{12}O_2NSCl_2Na$. Calculated %: N 4.60.

6. Preparation of N-acetylethanesulfodichloroanilide. 1 g of dichloroanilide and 0.5 ml of acetic anhydride were heated in a round bottomed flask with a reflux condenser for 4 hours on a paraffin bath at 140-160°. At the end of the reaction, the mixture was poured onto a large watch glass to evaporate the excess acetic anhydride. The residue crystallized as a compact yellow mass. The yield was 0.89 g (80.9%). The product was recrystallized from hot alcohol. The m.p. was 126-127° and it was insoluble in alkali. On acetylating 0.5 g of the dichloroanilide with acetyl chloride (0.39 ml) by heating on a boiling water bath, we isolated 0.5 g of a solid product, which was readily soluble in alkali and melted at 67° after recrystallization from alcohol and water, i.e., in this case acetylation did not occur and we completely isolated the original dichloroanilide. On acetylating the sodium salt of the dichloroanilide with acetyl chloride without any solvent, we isolated the acetyl derivative in 50% yield.

Found %: N 4.7. $C_{10}H_{11}O_3NSCl_2$. Calculated %: N 4.72.

7. Preparation of N-acetylbutanesulfodichloroanilide. We used 0.63 g of butanesulfodichloroanilide and 0.3 ml of acetic anhydride. The reaction was carried out similarly to the previous one. In this case the product crystallized only on cooling and scratching with a glass rod. The yield was 0.5 g (69.0%). It was recrystallized from alcohol and water. The crystals were colorless. The m.p. was 77-79°.

Found %: N 4.39. $C_{12}H_{15}O_3NSCl_2$. Calculated %: N 4.32.

8. Hydrolysis of ethanesulfodichloroanilide. Hydrolysis with alkali of various concentrations was not successful even on prolonged boiling. A hydrolysis was carried out with a mixture of concentrated sulfuric acid and water in the ratio 1:1. 0.5 g of ethanesulfodichloroanilide was suspended in 20 ml of sulfuric acid and boiled in a round bottomed flask with a reflux condenser for 8 hours. During the reaction, the ethanesulfodichloroanilide dissolved up. On cooling the solution and making it alkaline, we isolated the hydrolysis product-2,4-dichloroaniline. The yield was 0.2 g (66%). After recrystallization from water it melted at 62° (according to literature data: 62-63° [7]).

Found %: N 8.37. $C_6H_5NCl_2$. Calculated %: N 8.64.

9. Hydrolysis of butanesulfodichloroanilide. We used 1 g of butanesulfodichloroanilide and 20 ml of sulfuric acid, diluted 1:1. The experiment was as above. In this case the hydrolysis took longer (18-20 hours). We isolated the same hydrolysis product as with ethanesulfodichloroanilide, i.e., 2,4-dichloroaniline with m.p 61-63°.

SUMMARY

1. It was shown that chlorination of alkanesulfoanilides with elementary chlorine in CCl_4 as well as in alkaline medium resulted in the formation of alkanesulfo-2,4-dichloroanilides, in contrast to unsubstituted and alkyl substituted alkanesulfoamides as well as anilides of aromatic sulfo acids.

2. For the first time ethane-and butanesulfo-2,4-dichloroanilides were obtained and characterized; their sodium salts and N-acetyl derivatives were also obtained and characterized.

3. The position of the chlorine atoms in the aromatic nucleus was proved by the hydrolysis of the dichloroanilides to give 2,4-dichloroaniline.

LITERATURE CITED

[1] A. G. Kostsova, Trans. Voronezh State Univ. 8, 112 (1935).

[2] N. N. Melnikov, I. D. Sukhareva and F. Ya. Kavenoki, J. Appl. Chem. 18, 568 (1945).

[3] U.S.pat. 2394902; Ch. A., 40, 2847 (1946).

[4] F. D. Chattaway, J. Chem. Soc., 85, 1181 (1904).

[5] R. Z. Shriner, M. T. Coebel, C. S. Marial, J. Am. Chem. Soc., 54, 2470, (1932).

[6] A. G. Kostsova, J. Gen. Chem. 22, 1438 (1952).

[7] Beilst., XII, 621 (1929).

Received November 16, 1955

Voronezh State University

THE REACTION OF ACYLSULFANILYL CHLORIDE WITH 2-AMINOTHIAZOLE

II. INVESTIGATION OF THE REACTION OF CARBOMETHOXYSULFANILYL CHLORIDE WITH 2-AMINOTHIAZOLE

B. G. Yasnitsky and E. B. Dolberg

In the first paper [1] we gave the results of investigation of the reaction of di-(carbomethoxysulfanilyl)-aminothiazole with 2-aminothiazole in chlorobenzene, as one of the basic reactions occurring during the acylation of 2-aminothiazole with acylsulfanilyl chlorides. In the present paper we give data on the investigation of the acylation reaction which proceeds simultaneously in three principal directions, in accordance with the scheme given earlier. Organic solvents, chemically inert both to the starting materials as well as to the reaction products chlorobenzene and dichlorothane, were selected as reaction media. The choice of these solvents ensured a homogeneous reaction media. The choice of these solvents ensured homogeneous reaction as both aminothiazole and the sulfo chloride dissolved quite well in them, while the reaction products remain practically insoluble and this facilitated kinetic investigations. The inertness of the solvents used, as well as the use of 2-aminothiazole as the HCl-removing agent, eliminated a series of side reactions which occur, for example, when the same process is carried out in an aqueous medium in the presence of mineral bases (hydrolysis of sulfo chloride, acyl derivatives etc.). The use of chlorobenzene allowed investigations over a wide temperature range (25-130°).

EXPERIMENTAL

In the experiments we used 2-aminothiazole and the organic solvents described earlier [1]. The carbomethoxysulfanilyl chloride had m.p. 112-113° (from dichloroethane). According to analysis, the sulfo chloride contained 99.5-99.8% of organically bound chlorine. The reaction of carbomethoxysulfanilyl chloride with 2-aminothiazole was carried out in the following way. Into a three necked flask with a stirrer, a reflux condenser and a thermometer, placed in a thermostat, was loaded 100 ml of dry chlorobenzene and 5.0 g (0.05 moles) of 2-aminothiazole. When the temperature was established at 50°, 6.25 g (0.025 moles) of the sulfo chloride was introduced and the reaction mixture was kept at the same temperature for 15 minutes. We then proceeded as described earlier [1]. The mother liquors contained 3.60 g of unreacted aminothiazole (72.0% of that taken); 56% of the aminothiazole was consumed. The residue was washed with ethyl alcohol to remove traces of unreacted sulfo chloride. The weight of the dry residue was 7.0 g.. The mixture of acyl derivatives was analyzed as described earlier [1]. We found 1.40 g of the monoacyl derivative, 18%, and 5.04 g of the diacyl derivative, 38.3%. In the mixture of acyl derivatives there was 32.0 mol. % of the monoacyl derivative. On hydrolysis of the mixture we obtained 3.07 g of sulfanilamidothiazole, which accounted for all the charge.

The results of series of experiments, carried out as described but with various temperatures and times, are shown in the figures. As is obvious from curves 1 and 2 in Fig. 1, the proportion of the monoacyl derivative is strongly dependent on temperature, which results from the change in the ratio of the rates of reactions (1), (2) and (3) (see [1]). At a temperature of about 130°, the monoacyl derivative is almost the only one formed. That curves 1 and 2 and also 3 and 4 correspond quite closely, shows that the nature of the solvents investigated has an insignificant effect on the ratio of the rates of these reactions.

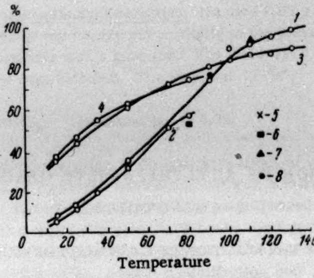


Fig. 1. The dependence of the results of acylation of 2-aminothiazole by carbomethoxysulfanilyl chloride on the temperature of the process, which was carried out for 1 hour. 1,2) composition of the acylation product in mol. % of monoacyl derivative ; 3,4) 2-aminothiazole consumed (in %) [1,3) in chlorobenzene, 2,4) in dichloroethane, 5) in acetone, 6) in benzene, 7) in toluene, 8) in a mixture of chlorobenzene and dichloroethane].

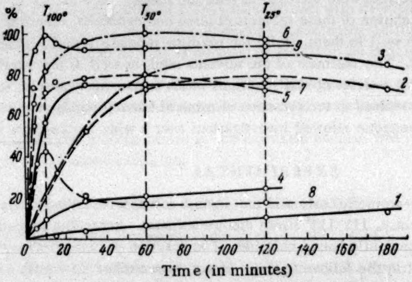


Fig. 2. Kinetics of acylation of 2-aminothiazole by carbomethoxysulfanilyl chloride in chlorobenzene. 1,4,7) amount of sulfo chloride (in % of that taken), consumed in the formation of the monoacyl derivative ; 2,5,8) the same, in the formation of the diacyl derivative ; 3,6,9) the same, in the formation of the total of the acyl derivatives [1,2,3) at 25°, 4,5,6) at 50°, 7,8,9) at 100°].

Examination of the kinetic curves in Fig. 2 shows that a point in time $T_{t°}$ ($T_{100°}$, $T_{50°}$, $T_{25°}$)- the maximum on the curves 3,6 and 9-is a characteristic for the process at the given temperature and appears to divide it into two periods. During the first period from 0 to T_t°, the maximum amount of the sulfo chloride is consumed to form the acyl derivatives according to equations (1) and (2) [1]: thus the monoacyl derivative is mainly formed according to equation (1) and the curves 1,4 and 7 increase quickly. The amount of diacyl derivative, formed according to equation (2), also grows quickly and reaches a maximum at the point T_t° (curves 2,5 and 8). In this period reaction (3) does not have appreciable significance as it is much slower (cf. Fig. 2 with Fig 1, report I).

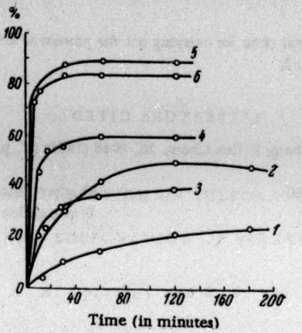


Fig. 3. Kinetics of acylation of 2-aminothiazole by carbomethoxysulfanilyl chloride.
1,3,5) molar percent of the monoacyl derivative in the acylation products; 2,4,6) aminothiazole consumed (in %) [1,2) at 25°, 3,4) at 50°, 5,6) at 100°].

In the second period of the reaction, after the point T_t°, reactions (1) and (2) are not important. The change in the system proceeds by equation (3) mainly; thus, as was shown earlier [1], the decrease in the amount of the diacyl derivative due to conversion into the monoacyl derivative is accompanied by a decrease in the overall amount of acyl derivatives. The ratio of the rates of build up of the monoacyl and diacyl derivatives, and consequently the molar proportions of them in the acylation products, depends not only on the temperature but also on the time that the process is carried out (Fig. 3). The amount of acylated 2-aminothiazole changes in accordance with the change in the molar percent of the monoacyl derivative; the former is proportional to the yield of sulfanilamidothiazole, obtained on hydrolysis of the acylation products. Consequently, the maximum yield of sulfanilamidothiazole may be obtained by carrying out the reaction for that period of time, which is necessary and sufficient for attaining the maximum amount of monoacyl derivative. As a rule, this time is greater than T_t°, which is necessary for the completion of reactions (1) and (2) (c.f. curve 9, Fig. 2 with curve 5, Fig. 3) and includes a short period, which is part of the time when the process is only according to scheme (3).

We undertook to determine the ratio of the rate constants of the reactions (1), (2) and (3) at various temperatures. The average, approximate data obtained showed that the rate constant of reaction (3) in the interval 25–130° was 2–3 orders less than the rate constants of reactions (1) and (2). Consequently, as long as there is sulfo chloride in the reaction system, reaction (3) has very little effect on the ratio of the reaction products. The latter is largely determined by the ratio of the rates of reactions (1) and (2). At 25° K_2 is almost 11 times greater than K_1, which leads to the formation of the diacyl derivative as the main reaction product. At 100° K_2 is almost 23 times less than K_1, in consequence of which the main product is the monoacyl derivative.

SUMMARY

1. It was established that the ratio of carbomethoxysulfanilylaminothiazole and di-(carbomethoxysulfoanilyl)-aminothiazole, acylation products of 2-aminothiazole with carbomethoxysulfanilyl chloride in inert solvents, depends mainly on temperature and duration of process and considerably less on the nature of the inert solvent.

2. The acylation process may be divided into two periods: in the first period the ratio of products is determined mainly by the rate constants of the more rapid reactions (1) and (2), in the second period by the rate constant of reaction (3). At 25° di-(carbomethoxysulfanilyl)-aminothiazole is the principal product; at 100° and higher–carbomethoxysulfanilylaminothiazole.

3. There is an increase not only in the relative amount of carbomethoxysulfanilylaminothiazole with a raise in temperature (up to 130°), but also an increase in the overall yield of acylation product, both on sulfo

chloride and aminothiazole. The optimal time for carrying out the process is the time when the greatest utilization of 2-aminothiazole is attained.

LITERATURE CITED

[1] B. G. Yasnitsky and E. B. Dolberg, J. Gen Chem. 26, 2046 (1956) (T. p. 2279).*

Received November 14, 1955

Kharkov Institute for the Scientific
Investigation of Chemical Pharmaceutics

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* T. P. = C. B. Translation pagination.

INVESTIGATION OF SULFONATION

XLI. HYDROLYSIS AND SULFONATION OF BENZENEDISULFONIC ACIDS

A. A. Spryskov and S. P. Starkov

In order to study the composition of sulfonation mixtures, formed by disulfonation of benzene, we undertook to investigate in the present work the conditions of hydrolysis (desulfonation) of isomeric benzene disulfonic acids and the conditions of their conversion into trisulfonic acid.

On the subject of hydrolysis of m-benzenedisulfonic acid, Friedel and Crafts [1] stated that it started to hydrolyze in phosphoric acid only at 330°. However, it was recently shown [2] that m-benzenedisulfonic acid can also hydrolyze at 234° in the presence of 85% sulfuric acid. There is no data on the hydrolysis of other isomers.

As regards the sulfonation of benzenedisulfonic acids, it is known that the meta-isomer may be sulfonated with polysulfate [3] at 280-300° or by heating with concentrated sulfuric acid on a naked flame until the mixture starts to effervesce [4]. Benzene with sulfuric acid and phosphorus pentoxide at 280-290° is also gradually sulfonated into trisulfonic acid [5]. Behrend and Mertelsmann [6] sulfonated sodium m-and p-benzenedisulfonates at 240-250°. Benzene trisulfonic acid is also formed together with the disulfonic acid [7] by heating benzene with fuming sulfuric acid at 235-245° in the presence of mercury.

EXPERIMENTAL

The experiments for studying the conditions under which the hydrolysis of isomeric benzenedisulfonic acids proceeds, were carried out in the following manner. A calculated amount of sulfuric acid and water was added to the sample of free benzenedisulfonic acid in the test tube. Three test tube with ortho-, meta-and para-isomers were sealed and heated simultaneously in an Eikman apparatus. After heating, the sulfuric acid content in the reaction mixture was determined by a gravimetric method. The increase in the amount of sulfuric acid relative to the sample taken enabled us to calculate the amount of disulfonic acid, hydrolyzed to the monosulfonic acid. The experimental results, given in Table 1, show that o-benzenedisulfonic acid was hydrolyzed more readily than the other isomers, the para-isomer with most difficulty and the meta-isomer in-between the two. The experiments also made clear that the ortho-isomer started to hydrolyze noticeably in 80% sulfuric acid at a temperature somewhat lower than 180°. The hydrolysis of the meta-isomer became noticeable at 195° while that of the para-isomer only at 206°.

It was shown earlier by one of us and Ovsyankina [2], using a whole series of aromatic sulfonic acids with substituents in the nucleus, that a sulfonic acid with a substitutent in the meta-position was the most stable isomer to desulfonation. However, sulfonic acids investigated in this work were with substitutents of the I order in the nucleus, with the exception of sulfobenzoic acid, the relative stability of the meta-and para-isomers of which remained unclear. The experimental results, given in Table 1, suggest that the para-isomer is the most stable with a substituent of the II order in the nucleus, while the meta-isomer has an intermediary position.

Experiments on the hydrolysis of sulfobenzoic acids were again carried out in the present work, using the methods described above. The results of these experiments, given in Table 2, showed that p-sulfobenzoic acid as well as p-benzenedisulfonic acid were the most stable isomers, while the meta-isomer has an intermediary position.

Before carrying out the experiments described, the benzenemonosulfonic acid was heated with 85% sulfuric acid at 195° in a sealed tube. Titration with 0.1 N alkali showed that after 10, 15 and 20 hours the overall acidity of the reaction mixture did not change, i.e., the sulfonic acid was not being sulfonated into the disulfonic acid. However, at 210° the sulfonation of the monoacid proceeded at a considerable rate, which can be seen by comparing the results of experiments 78 and 76 in Table 1. The amount of hydrolyzed acid not only did not increase in the latter experiment, even though heated longer, but even decreased in the experiment with the ortho-isomer due to isomerization of the ortho-acid, which proceeded by hydrolysis and resulfonation.

The same may be observed in the experiments in Table 2.

An increase in heating time from 10 to 20 hours did not double the amount of sulfobenzoic acid hydrolyzed, as the sulfonation of the benzoic acid formed proceeds together with the hydrolysis.

The sulfonation of three isomeric benzenedisulfonic acids was carried out in the following way. A portion of disulfonyl chloride was mixed with 60% fuming sulfuric acid and heated in a sealed tube in an Eikman apparatus. After heating, twice the volume of chlorosulfonic acid was added to the mixture and the reaction mixture was again heated at 145-150° for 1/2 an hour in an open test tube. The cooled mixture was poured onto ice, the precipitate separated, washed, dried and the melting point of the chloride obtained determined.

TABLE 1

Hydrolysis of Benzenedisulfonic Acids in the Presence of Sulfuric Acid

Experiment number	Benzenedisulfonic acid	Moles of water taken per mole of sulfonic acid	Sulfuric acid concentration in the mixture (%)	Temperature	Heating time (hours)	Acid hydrolysed in % of that taken)
71	ortho-	9.0	85.0	163°	10	0
65	ortho-	9.4	80.2	180	10	15.2
	meta-	8.9	79.7	180	10	0
	para-	8.9	78.8	180	10	0
63	ortho-	9.6	77.3	195	10	24.3
	meta-	9.6	79.4	195	10	1.1
	para-	9.8	79.0	195	10	0
72	ortho-	9.1	80.2	206	10	47.1
	meta-	9.4	80.1	206	10	9.2
	para-	9.3	79.9	206	10	2.6
78	ortho-	9.2	79.8	210	10	54.7
	meta-	9.0	80.1	210	10	14.3
	para-	8.9	79.1	210	10	4.6
76	ortho-	9.1	88.1	210	20	28.7
	meta-	9.5	79.0	210	20	19.4
	para-	8.1	78.2	210	20	3.3

In a number of experiments the sulfonation mixture poured onto ice was neutralized with barium carbonate. Then a calculated amount of soda was added and the solution of sodium salts of sulfonic acids was filtered and evaporated to dryness. The salts, dried at 130-150°, were converted into chlorides by heating with twice their weight of phosphorus pentachloride at 110-175° for 25 minutes.

The experimental results, given in Table 3, show that m-benzenedisulfonic acid practically does not sulfonate at 150 and 180° as the m.p. of the dichloride (60°) taken for the reaction changed very little.

Sulfonation at a considerable rate began ~200°. Thus, by heating at 205° for 4 hours 1,3,5-benzenetrisulfonyl chloride was formed with a m.p. of 175° instead of the m.p. of 190° of pure trichloride. The same product was obtained by raising the sulfonation temperature to 228° for 1/2 hours heating. But a better product with m.p. 183° was obtained by heating for 4 hours. Further increase of the sulfonation time did not improve the quality of the product. After five crystallizations from benzene, the product from experiment 174 had a m.p. of 190-191°.

TABLE 2

Hydrolysis of Sulfobenzoic Acids in the Presence of Sulfuric Acid at 202°

Experiment number	Sulfobenzoic acid	Moles of water taken per mole of sulfonic acid	Sulfonic acid concentration in the mixture (in %)	Heating time (in hours)	Acid hydrolysed (in % of that taken)
160	ortho-	4.3	84.8	10	23.9
	meta-	4.3	81.6	10	8.9
	para-	4.9	78.6	10	3.8
161	ortho-	4.6	87.4	20	23.1
	meta-	4.6	79.7	20	10.2
	para-	4.4	79.5	20	3.9

The para-dichloride was not changed by a short period of heating with fuming sulfuric acid at 228°, but the m.p. of the product obtained by increasing the duration of the process, to 24 hours, decreased to 104°. A single crystallization of this product from benzine gave again almost pure para-dichloride with m.p. 136-137°.

The ortho-isomer also changed little when heated for a short time with fuming sulfuric acid, while a long heating period at 228° gave an uncrystallizable product.

TABLE 3

Sulfonation of Benzenedisulfonyl Chlorides with 60% Fuming Sulfuric Acid

Experiment number	Taken		heating time	Temperature	Melting points of chlorides obtained from the isomers		
	disulfonyl chloride (in g)	fuming sulfuric acid (ml)			ortho-	meta-	para-
18	1	1.5	4	150°		56°	
20	0.51	1	4	180		52	
33	0.25	1.5	4	205		175	
32	0.25	1.5	0.5	228	137°	175	136°
30, 31	0.25	1.5	1	228		179—181	136
82—84	0.25	1.5	1.5	228	136	180	124
172	2.2	6	2	225	115 *		
22, 25	0.5	1.5	4	228		183	110
27	0.25	1.5	4	230			108
174	2.0	6	8	229		178—184	
177, 178	0.25	3	12	231	Soft *		107
177′, 178′	0.25	3	24	231	Soft *		104
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* Chlorides obtained through salts with PCl_5.

The experiments showed that even when the ortho-and para-isomers were heated for a long time with fuming sulfuric acid, no isomerization of them was observed with formation of m-disulfonic acid, as the latter is readily sulfonated to trisulfonic acid under the conditions described. Trisulfonyl chloride could have been readily detected in the sulfonation products of ortho-and para-isomers, as it is dissolved with considerably more difficulty than ortho-and para-disulfochlorides.

Preparations. We prepared pure benzenedisulfonic acids using the methods given earlier [8]. o-Sulfobenzoic acid with m.p. 67.5° was prepared from anthranilic acid through dithiosalicylic acid [9]; p-sulfobenzoic acid was obtained by oxidizing p-toluene sulfonic acid. The temperature varied within the range of ± 2° from the one indicated during heating of the sealed tubes in the Eikman apparatus.

SUMMARY

It was found that the hydrolysis of isomeric sulfonic acids of the benzene series with substituents of the second type in the nucleus (–SO_3H, -COOH) proceeded at different rates. The para-isomer is the most stable to hydrolysis, the meta-isomer has an intermediate position while the ortho-isomer is the most reactive. o-Benzenedisulfonic acid starts to hydrolyze noticeably in 80% sulfuric acid at a temperature somewhat lower than 180°, the meta-isomer at 195° and the para-isomer at 205°.

m-Benzenedisulfonic acid is sulfonated with 60% fuming sulfuric acid at a considerable rate at 200° and rapidly at 230°. The ortho-and para-isomers change very slowly when heated with fuming sulfuric acid at 200-230°, but no products of their sulfonation or isomerization were detected.

LITERATURE CITED

[1] C. Friedel, J. Crafts, C.r., 109, 95 (1889).

[2] A. A. Spryskov and N. A. Ovsyankina, J. Gen. Chem. 24, 1810 (1954) (T. p. 1777)*.

[3] German pat. 113784; Zbl., 1900, II, 883.

[4] C. L. Jackson, J. F. Wing, Am. Chem. J., 9, 329 (1887).

[5] C. Senhofer, Ann. Chem. Pharm., 174, 243 (1874).

[6] R. Behrend, M. Mertelsmann, Lieb. Ann., 378, 361 (1911).

[7] Fr. Fichter, E. Stocker, Helv. Chim. Acta, 7, 1077, Anm. (1924).

[8] A. A. Spryskov and S. P. Starkov, J. Gen.Chem. 26, 2607 (1956).

[9] Reagents and Preparations for Laboratories, Ed. V. V. Longinov (State United Sci. Tech. Press, 1938), 312.

Received November 9, 1955

Ivanov Institute of Chemistry and Technology

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* T. p. = C. B. Translation pagination.

SULFONIC ACIDS OF SULFONES AS SIDE PRODUCTS IN SULFONATION PROCESSES

III. BEHAVIOR OF DIPHENYL SULFONE AND ITS SULFONIC ACIDS UNDER THE ACTION OF SULFURIC ACID*

A. P. Shestov and N. A. Osipova

As was shown in the first paper [1], sulfonic acids of diphenyl sulfone are formed in large amounts by sulfonating benzene with fuming sulfuric acid. Diphenyl sulfone is formed under certain conditions by the action of aqueous sulfuric acid on benzene; however, the process of formation of sulfonic acids of sulfone was not established as present. The behavior of diphenyl sulfone when treated with fuming sulfuric acid or sulfuric acid is not clear. On the basis of old papers [2] it had been assumed that diphenyl sulfone underwent cleavage under these conditions with the formation of benzenemonosulfonic acid.

As we had a number of methods at our disposal for the determination of sulfonic acids of sulfones and among them polarography [3], we decided to carry out an investigation of the behavior of diphenyl sulfone and its sulfonic acids under the action of sulfuric acid.

The diphenyl sulfone was subjected to sulfonation at a temperature of 90° with different concentrations of fuming sulfuric acid (containing from 20 to 65% of SO_3) with an excess of SO_3 sufficient to introduce two sulfonyl groups; it was established that diphenyl sulfone was quite readily converted into a sulfonic acid which contained two sulfonic groups for each diphenyl sulfone molecule.

The monosulfonic acid of diphenyl sulfone was formed by treating diphenyl sulfone with fuming sulfuric acid containing an amount of SO_3 sufficient for forming only one sulfonyl group.

Even the first experiments of sulfonating diphenyl sulfone with aqueous sulfuric acid showed that diphenyl sulfone behaves differently in this medium and, apparently, a large proportion of it is cleaved with the formation of benzenesulfonic acids. Diphenyl sulfone was dissolved quite rapidly when placed into sulfuric acid (87-96%) even in the cold; however, when the mass was diluted with water almost all the original diphenyl sulfone separated. Diphenyl sulfone underwent a more extensive conversion with the formation of water soluble reaction products at a temperature of the order of 170-200°.

A polarographic determination of sulfonic acids of sulfones in the sulfonation mixture, obtained by the action of 85-98% sulfuric acid on diphenyl sulfone at 230°, showed that the diphenyl sulfone mainly underwent cleavage with the formation of benzenesulfonic acids. A considerably smaller amount of sulfonic acids of diphenyl sulfone was formed (5-18% of the original diphenyl sulfone, depending on the concentration of sulfuric acid).

The separation with ligroin of the sulfonyl chlorides obtained by the usual method from the reaction mixture, allowed the detection of both benzene m-disulfonyl chloride and the 3,3'-disulfonyl chloride of diphenyl sulfone in corresponding amounts.

Sulfonic acids of benzene and diphenyl sulfone of other degrees of sulfonation were not separated as they could not have been in large quantities considering the high sulfonation temperature, and furthermore, the principal problem interesting us was whether diphenyl sulfone was sulfonated or cleaved by the action of aqueous sulfuric acid.

As subsequent experiments showed, the sulfonyl group already in the diphenyl sulfone molecule, under the conditions studied, strengthens the bonds of the SO_2 group with the benzene nuclei and cleavage occurs to a lesser degree. Thus, up to 70% of the disulfonic acid of diphenyl sulfone is formed by the action of 98% sulfuric acid at 230° on the monosulfonic acid of diphenyl sulfone. The disulfonic acid of diphenyl sulfone hardly cleaves under the action of sulfuric acid at a temperature of 230°.

EXPERIMENTAL

The diphenyl sulfone used in the investigations was obtained by treating a large excess of benzene with 65% fuming sulfuric acid at a temperature below 60°. The diphenyl sulfone was sublimed by passing nitrogen over its molten surface. The sublimed product was recrystallized from alcohol. The diphenyl sulfone obtained had m.p. 124° (literature data: 124 and 128° for various modifications [4]).

Chemically pure fuming sulfuric acid was used.

Sulfonation of diphenylsulfone with fuming sulfuric acid. a) Sulfonation of diphenyl sulfone into the disulfonic acid (experiments 1-4). The diphenyl sulfone was treated with a large excess of 20 and 63% fuming sulfuric acid at 90° (introduced at 30° and kept at 90° for 3 hours). The following were prepared from the sulfonic acid using the usual methods: barium salts (in which the percent of barium was determined), sulfonyl chloride and sulfamide. The data obtained are given below (Table 1).

The barium salt of diphenyl sulfone disulfonic acid contained 26.74% Ba.

The sulfonyl chloride, without recrystallization, had m.p. 171°. A product with m.p. 180.5-181.0° was obtained after several recrystallizations from chloroform. The m.p. of diphenyl sulfone disulfonyl chloride is given as 175-176° in the literature [5].

TABLE 1

Experiment number	Charge of diphenyl sulfone (in g)	Charge of fuming sulfuric acid			Analysis of barium salts of sulfonic acids		
		g	% SO_3	moles of SO_3 per mole of sulfone	weight of Ba-salt (in g)	weight of $BaSO_4$ (in g)	% of Ba in barium salt
1	2.33	17.65	19.6	3.7	0.3118	0.1426	26.91
2	1.0	7.85	20.0	4.3	0.4108	0.1890	27.07
3	1.0	7.85	20.0	4.3	0.3064	0.1390	26.70
4	20.0	121.7	63.0	10.4	—	—	

Found %: C 34.28; H 2.19; Cl 16.83; S 23.24. $C_{12}H_8O_6Cl_2S_3$. Calculated %: C 34.70; H 1.94; Cl 17.08; S 23.16.

The amide of diphenyl sulfone disulfonic acid with m.p. 249.6-250.1° (in the literature 242.0° [5]) was obtained from diphenyl sulfone disulfonyl chloride by the usual method.

Found %: C 38.60; H 3.27; N 7.16; S 25.70. $C_{12}H_{12}O_6N_2S_3$. Calculated %: C 38.29; H 3.22; N 7.44; S 25.56.

b) Sulfonation of diphenyl sulfone into monosulfonic acid (experiment 5). 118 g of diphenyl sulfone with m.p. 124° was mixed with 50.2 g of 100% sulfuric acid and then 63.3 g of fuming sulfuric acid, containing 64.35% of SO_3 (0.94 mole of SO_3 per mole of diphenyl sulfone), was added dropwise. After a gradual increase in temperature to 90° it was maintained at 90° for 3 hours. The sulfonyl chloride was obtained by the usual method from the sulfonic acid and after recrystallization from ligroin it had m.p. 96° (in the literature 98-99° [6]).

The sulfoamide obtained from the sulfonyl chloride had m.p. 155.5-156° (in the literature 154° [6]) after recrystallization from water.

Found %: C 47.95; H 3.77; S 21.88. $C_{12}H_{11}O_4NS_2$. Calculated %: C 48.46; H 3.73; S 21.57.

Reaction of diphenyl sulfone and its mono-and disulfonic acids with aqueous sulfuric acid. a) Determination of the temperature at which diphenyl sulfone is converted into a water soluble compound (experiments 6-9). Diphenyl sulfone was dissolved in aqueous sulfuric acid and the temperature at which it was converted into a water soluble compound was determined.

As the data in Table 2 show, the reaction products became completely soluble in water at 190°.

TABLE 2

Experiment number	Charge			Temperature	Time (in hours)	Solubility of the sulfonation mixture in water
	Diphenyl sulfone (in g)	H_2SO_4 (in g)	% H_2SO_4			
6	5	25	96	50°	1/3	Incomplete
			96	100	1/3	
			96	150	1/3	
			96	190	2	Complete
7	3	30 ml	87	190	5	Incomplete
			87	190	10	
			87	190	30	Complete
8	3	30 ml	92	180	1	Becomes turbid with water
9	1	10 ml	96.3	190	3	Complete

b) The isolation of the reaction products of diphehyl sulfone with aqueous sulfuric acid (experiment 10). 20 g of diphenyl sulfone was dissolved with mixing in 99.5 g of 98.7% sulfuric acid (10.9 moles of sulfuric acid per mole of diphenyl sulfone).

The homogeneous mass was poured into ampules. The sealed ampules were heated at 230° for 5 hours. The sulfonic acids were converted into the sulfonyl chlorides by the usual method.

7 g of sulfonyl chlorides was washed on a Schott filter with 3.5 liters of ligroin. 0.52 g of diphenyl sulfone 3,3'-disulfonyl chloride remained on the filter. After recrystallization from chloroform it had a m.p. 178.5-179°.

Found %: C 34.71; H 2.05; Cl 17.41; S 22.30. $C_{12}H_8O_6Cl_2S_3$. Calculated %: C 34.70; H 1.94; Cl 17.08; S 22.16.

The chloride did not depress the melting point of the chloride which we obtained earlier.

The filtrate was evaporated in vacuum at 40° and the dry residue was recrystallized from ligroin. The crystals obtained were white with m.p. 63° and corresponded to the literature data [7] for benzene-m-disulfonyl chloride.

Found %: C 26.6; H 1.68; Cl 25.85; S 23.0. $C_6H_4O_4S_2Cl_2$. Calculated %: C 26.19; H 1.46; Cl 25.78; S 23.31.

It did not depress the melting point of benzene-m-disulfonyl chloride.

c) Separation of the reaction products of diphenyl sulfone monosulfonic acid with aqueous sulfuric acid (experiment 11). 2.72 g of diphenyl sulfone monosulfonyl chloride with m.p. 96° was taken for the experiment. The monosulfonic acid, obtained from it by saponification, was mixed with 9.6 g of 97.8% sulfuric acid (11.1 moles of sulfuric acid per mole of diphenyl sulfone monosulfonic acid) and heated in an ampule at 230° for 5 hours. The sulfonic acids were converted into sulfonyl chlorides by the usual method. The latter were separated with ligroin in the cold. 48% of diphenyl sulfone 3,3'-disulfonyl chloride was found on the filter with a m.p. 171-171.5°. After recrystallization from chloroform the product had m.p. 179-180°.

Found %: C 34.82; H 1.95. $C_{12}H_8O_6Cl_2S_3$. Calculated %: C 34.70; H 1.94.

After distilling off the ligroin from the mother liquor (in vacuum at 40°) a product remained with m.p. 58.5-59.5° (after recrystallization) and with an elementary composition corresponding to benzene-m-disulfonyl chloride.

Found %: C 26.44; H 1.41. $C_6H_4O_4Cl_2S_2$. Calculated %: C 26.19; H 1.46.

d) Separation of reaction products of diphenyl sulfone disulfonic acid with aqueous sulfuric acid (experiment 12). The starting material was diphenyl sulfone 3,3'-disulfonyl chloride with m.p. 180-181° of which 4.36 g was taken. The disulfonic acid obtained from it by saponification was mixed with 20.18 g of 98.4% sulfuric acid (20 moles of sulfuric acid per mole of diphenyl sulfone disulfonic acid) and heated in an ampule at 230° for 5 hours. The sulfonic acids were converted into sulfonyl chlorides by the usual method. The latter were separated by ligroin.

84.3% diphenyl sulfone 3,3'-disulfonyl chloride was found of the material taken for sulfonation. This sulfonyl chloride remained on the filter and had a m.p. 179.5-180° without recrystallization, and corresponded in composition to diphenyl sulfone disulfonyl chloride.

Found %: C 35.11; H 2.13; Cl 16.26. $C_{12}H_8O_6Cl_2S_3$. Calculated %: C 34.70; H 1.94; Cl 17.08.

Polarographic analysis of the sulfonation mixture obtained by treating diphenyl sulfone and its mono- and disulfonic acids with sulfuric acid. To determine more accurately the degree of formation of sulfonic acids of diphenyl sulfone, a series of sulfonation experiments were carried out, analogous to those described above, in which the sulfonation mixture was analyzed polarographically.

In all the given polarograms the aqueous solutions of the corresponding sulfonation mixtures taken were made alkaline with tetraethylammonium hydroxide. 0.05 m $N(C_2H_5)_4I$ was used as base. The polarograms were taken at a 3.8 V, 1/100 sensitivity and with a zero abscissa. The values given for the half wave potentials are everywhere referred to a saturated calomel electrode.

The polarogram of the mixture of benzene-m-disulfonic acid and diphenyl sulfone 3,3'-disulfonic acid given in the first paper [1] was used as the standard curve.

The data from experiments 13–17 are given in Table 3 and the corresponding polarograms* in Figs. 1–5.

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* The applied voltage ($-\varphi$) is plotted on the abscissa and the strength of the current (I), on the ordinate.

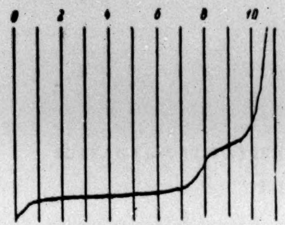

Fig. 1. Treatment of diphenyl sulfone with 85.09% sulfuric acid (experiment 13).

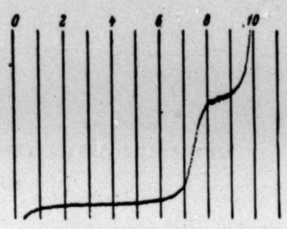

Fig. 2. Treatment of diphenyl sulfone with 95.17% sulfuric acid (experiment 14).

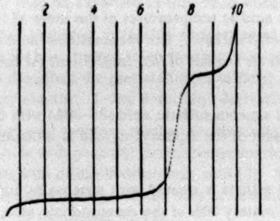

Fig. 3. Treatment of diphenyl sulfone with 98.3% sulfuric acid (experiment 15).

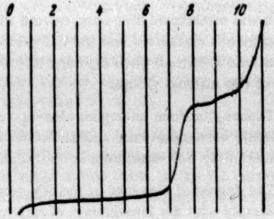

Fig. 4. Treatment of diphenyl sulfone monosulfonic acid with 98.3% sulfuric acid (experiment 16).

TABLE 3

Experiment number	Taken for the sulfonation			Moles of H_2SO_4 per mole of sulfone	Sample of sulfonation mixture for analysis* in g	Obtained		Calculated percent of diphenyl sulfone disulfonic acid
	Diphenyl sulfone (in g)	H_2SO_4 (in g)	% H_2SO_4			h (in mm)	$-\varphi_{1/2}$ (V)	
13	0.5000	2.65	85.09	10	0.8954	12.0	1.82	5.18
14	0.5000	2.37	95.17	10	1.0134	41.5	1.78	14.43
15	2.0000	10.0	98.3	9.2	1.0182	51.0	1.78	18.45
16	Diphenyl sulfone monosulfonyl chloride 0.5000	3.15	98.3	20	0.3818	39.5	1.77	70.53
17	Diphenyl sulfone disulfonyl chloride 1.0000	4.7	98.3	19.6	0.3706	55.0	1.78	98.95

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* The samples of the sulfonation mixture after neutralization and addition of base were made up to a volume of 100 ml.

Fig. 5. Treatment of diphenyl sulfone disulfonic acid with 98.3% of sulfuric acid (experiment 17).

SUMMARY

1. It was established that when treated with fuming sulfuric acid at temperatures of the order of 100°, diphenyl sulfone is converted into the 3,3'-disulfonic acid of diphenyl sulfone. The monosulfonic acid of diphenyl sulfone is formed when diphenyl sulfone is sulfonated with an amount of SO_3 insufficient for the formation of two sulfonyl groups.

2. Diphenyl sulfone undergoes cleavage under the action of aqueous sulfuric acid (85-98%) with the formation of mainly benzenesulfonic acids. Besides this, a certain amount of the diphenyl sulfone is sulfonated with the formation of the 3,3'-disulfonic acid of diphenyl sulfone.

3. The degree of cleavage at the SO_2 group when diphenyl sulfone is treated with aqueous sulfuric acid, decreases sharply with the introduction of sulfonyl groups. Approximately 30% of the monosulfonic acid of diphenyl sulfone undergoes cleavage, while the disulfonic acid of diphenyl sulfone is hardly cleaved under the given conditions.

LITERATURE CITED

[1] A. P. Shestov, J. Gen. Chem. 26, 1219 (1956) (T. p. 1379).*

[2] H. Gericke, Ann. Chem. u. Pharm., 100, 207 (1856); A. Kekule, Z. Chem., 11, 193 (1868).

[3] E. S. Levin and A. P. Shestov, Proc. Acad. Sci. USSR 96, 999 (1954).

[4] V. J. Mikeska, N. T. Farinacci, M. T. Bogert, J. Am. Chem. Soc., 58, 1869 (1936).

[5] R. Otto, A. Rossing, Ber., 19, 3126 (1886).

[6] R. Otto, Ber., 19, 2420 (1886).

[7] M. J. J. Polak, Rec. trav. chim., 29, 427 (1900).

Received October 20, 1955

State Institute for the Scientific Investigation of
Organic Intermediate Products and Dyes

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* T. p. =C. B. Translation pagination.

SULFANYL DERIVATIVES OF NATURAL AMINO ACIDS AND THEIR ANALOGS

Yuan Chen-e and M. N. Shchukina

The synthesis of sulfanyl derivatives of natural acids is of definite interest as physiologically active materials may be expected, as was found when the sulfanyl residue was combined with p-aminobenzoic acid [1].

The number of sulfamide derivatives of this type known up to now is small, while their biological study has been mainly limited to an investigation of their activity in relation to streptococci. A series of authors [2] have described the preparation of sulfanyl derivatives of glycine, alanine, tyrosine, valine, leucine, norleucine and phenylalanine. 1-and 4-sulfanyl derivatives of lysine were synthesized by us [3].

The most common method for obtaining p-aminobenzenesulfonylamino acids is by condensation of the amino acids with p-acetyl-aminobenzenesulfonyl chloride by the Shotten-Baumann method followed by hydrolysis with dilute hydrochloric acid [4]. The sulfanyl derivatives of amino acids, which are unstable to acidic and alkaline hydrolysis, may be obtained by acylation with p-nitrobenzoyl chloride followed by the reduction of the nitrogroup [5].

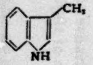
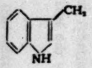
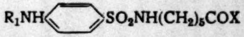
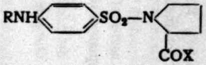
We carried out the synthesis of a series of p-aminobenzenesulfonylamino acids and their derivatives. The properties and analyses of the new compounds obtained by us are given in the table.

For the synthesis we used mainly the method of acylation with p-acetylaminobenzenesulfonyl chloride. p-Carbomethoxyaminobenzenesulfonyl chloride could not be used due to the difficulty of saponifying the p-carbomethoxy compounds obtained.

In preparing p-aminobenzenesulfonylaniline described by Mazza [6], we synthesized a material which melted 40° higher than that described by the author. We synthesized a number of derivatives from this material that have not been described in the literature: the ethyl ester, amide, hydrazide and hydrazones. From d,l-serine we obtained α-(p-aminobenzenesulfamido)-β-hydroxypropionic acid which has not been described in the literature. It is interesting to note that the N-sulfanyl derivative of serine does not react in the same manner as α, β-diaminohydroxy acids and 1,2-amino alcohols acylated with carboxylic acid radicals in which the acyl group has the capacity of migrating from nitrogen to oxygen under the influence of acids. This is confirmed by the fact that the hydroxyl group remains free after such treatment and may be readily substituted by chlorine on reaction with thionyl chloride. These investigations were carried out with the methyl ester of α-(p-acetylaminobenzenesulfamido)-β-hydroxypropionic acid, which was synthesized through its silver salt as it was impossible to eliminate saponification of the acetyl when esterifying with alcohol.

The methyl ester of α-(p-acetylaminobenzenesulfonamido)-β-chloropropionic acid was converted into mercapto and alkylmercapto derivatives by potassium xanthogenate or mercaptides. After saponification, previously unknown mercapto and alkylmercapto analogs of the sulfanyl derivative of serine were obtained. These alkyl derivatives we also synthesized by another method – by the action of alkyl iodides on the mercapto compound in the presence of alkali.

In the preparation of the N-sulfanyl derivative of cysteine, oxidation of the material occurred with the formation of the disulfide. A good yield of N-(p-acetylaminobenzenesulfonyl)-cysteine was obtained by carrying out the reaction in a current of nitrogen and in the presence of 2% hydrosulfite, while N-(p-aminobenzenesulfonyl)-cysteine was obtained by saponifying it and then treating the acidic solution with metallic zinc.

Sample No.	R	R₁	X	Melting point	Empirical formula	Calculated (%)			Found (%)			Obtained similiarly to experiment
						C	H	N	C	H	N	
16	$(CH_3)_2CHCH_2$	H	$NHNH_2$	170—71°	$C_{12}H_{20}O_3N_4S$	48.00	6.67	—	48.00	6.81	—	3
17		$COCH_3$	OH	238—39	$C_{19}H_{19}O_5N_3S$	56.86	4.74	10.47	56.95	4.84	9.90	7
18		H	OH	188—90	$C_{17}H_{17}O_4N_3S \cdot HCl$	*	—	10.62	*	—	10.79	8
												
19		$COCH_3$	OH	146—47°	$C_{14}H_{20}O_5N_2S$	51.22	6.09	8.54	51.31	6.10	8.44	7
20		H	OH	134	$C_{12}H_{18}O_4N_2S$	50.35	6.29	9.79	50.59	6.00	10.02	8
21		H	OC_2H_5	94	$C_{14}H_{22}O_4N_2S$	53.50	7.01	8.91	53.45	7.13	9.16	4
												
22	$COCH_3$		OH	228—29°	$C_{13}H_{16}O_5N_2S$	**	—	8.97	**	—	8.86	7
23	H		OH	126—28	$C_{11}H_{14}O_4N_2S \cdot H_2O$	45.83	5.56	9.72	45.89	5.63	9.63	8
24	H		OC_2H_5	145—47	$C_{13}H_{18}O_4N_2S$	52.68	6.04	9.40	52.58	6.24	9.50	4

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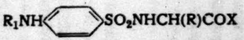
* For № 18 Found % Cl 8.98; Found 8.81.

** For № 22 Calculated % S 10.25; Calculated 10.26.



Sample No.	R	R_1	X	Melting point	Empirical formula	Calculated (%)			Found (%)			Obtained similiarly to experiment
						C	H	N	C	H	N	
1	CH_3	$COOCH_3$	OH	206—206.5°	$C_{11}H_{14}O_6N_2S$	*	—	9.27	*	—	9.22	1
2	CH_3	H	OH	152 **	$C_9H_{12}O_4N_2S$	*	—	11.48	*	—	11.52	8
3	CH_3	H	$NHNH_2$	138—40	$C_9H_{14}O_3N_4S$	41.86*	5.43	21.71	42.14*	5.55	21.46	3
4	$C_6H_5CH_2$	$COCH_3$	OH	221 ***	$C_{17}H_{18}O_5N_2S$	*	—	7.73	*	—	7.52	7
5	$C_6H_5CH_2$	H	OC_2H_5	120—21	$C_{17}H_{20}O_4N_2S$	58.62	5.75	8.05	58.41	5.66	8.24	4
6	$C_6H_5CH_2$	H	$NHNH_2$	192—93	$C_{15}H_{18}O_3N_4S$	—	—	16.76	—	—	16.64	3
7	l-$C_4H_9SCH_2$	$COCH_3$	OH	175—76	$C_{15}H_{22}O_5N_2S_2$ ****	48.13	5.88	7.49	48.45	5.78	7.38	15
8	l-$C_4H_9SCH_2$	H	OH	150—51	$C_{13}H_{20}O_4N_2S_2$ *****	47.00	6.02	8.43	46.99	5.92	8.53	16
9	$C_{11}H_{13}O_5N_2S_3CH_2$	$COCH_3$	OH	201—2	$C_{22}H_{26}O_{10}N_4S_4$	41.64	4.10	8.83	41.19	4.13	8.63	7
10	$C_9H_{11}O_4N_2S_3CH_2$	H	OH	164—66	$C_{18}H_{22}O_8N_4S_4 \cdot H_2O$	38.04	4.23	9.85	38.30	4.38	9.68	8
11	$(CH_3)_2CSH$	$COCH_3$	OH	224—29	$C_{13}H_{18}O_5N_2S_2$	45.09	5.20	8.09	44.94	4.97	8.05	12—II
12	$(CH_3)_2CSH$	H	OH	184—86	$C_{11}H_{16}O_4N_2S_2$	43.42	5.26	9.21	43.63	5.12	9.29	12—II
13	$CH_3SCH_2CH_2$	$COCH_3$	OH	149—51	$C_{13}H_{18}O_5N_2S_2$	45.09	5.20	8.09	45.16	5.33	8.00	7
14	$CH_3SCH_2CH_2$	H	OH	159—63	$C_{11}H_{16}O_4N_2S_2$	43.42	5.26	9.21	43.62	5.10	9.14	8
15	$(CH_3)_2CHCH_2$	H	OC_2H_5	105—6	$C_{14}H_{22}O_4N_2S$	53.50	7.00	8.92	53.88	6.89	8.97	4

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* For Nos. 1—4 calculated % S, respectively; 10.60, 13.11, 12.40, 8.84; found %: S 10.61, 12.95, 12.57, 8.57.

** Literature data: m. p. 107—108° [6].

*** Literature data: m. p. 205—206° [7], 218—219° [8].

**** $[\alpha]_D^{20}$ +14.95 (1% alcohol solution)

***** $[\alpha]_D^{20}$ —18.6 (1% solution in 2 N HCl).

This compound is the first example of a sulfanyl derivative of an amino acid with a free sulfhydryl group. Using an analogous method we synthesized sulfanyl derivatives of dimethylcysteine.

We treated cysteine with sodium in liquid ammonia and then alkyl iodides to synthesize the optically active S-alkylated N-sulfanyl cysteines.

Of the number of derivatives of amino acids containing 6 carbon atoms, we synthesized sulfanyl-ϵ-leucine, which had not yet been described, its ester, hydrazide and hydrazones, as well as analogous derivatives of sulfanyl substituted leucine and norleucine. We synthesized d,l-leucine for our work in a 36% yield using Stadnik and Zelinsky's method which had not been used previously for obtaining this amino acid.

We used a new, simpler method to obtain the sulfanyl derivative of norleucine – the reaction of the potassium salt of the sulfamide and α-bromocaproic acid in the presence of potassium iodide in a dilute alcohol solution.

We synthesized derivatives of proline and tryptophan of the heterocyclic amino acid series. It should be noted that the indole imino group of tryptophan does not react with p-acetylaminobenzenesulfonyl chloride under Shotten-Baumann conditions.

EXPERIMENTAL

1. N-(p-Carbomethoxyaminobenzenesulfonyl)-glycine. 37.5 g of p-carbomethoxyaminobenzenesulfonyl chloride was gradually added with stirring to a solution of 11.25 g of glycine in 20 ml of 40% caustic soda solution and 50 ml of water. The reaction was kept slightly alkaline by the periodic addition of 40% caustic soda solution. After 3 hours stirring, the reaction mixture was treated with charcoal and the filtrate was acidified with hydrochloric acid (to Congo). The precipitate melted at 169 – 170° after recrystallization from 60% alcohol. The colorless, crystalline substance was soluble in alcohol and insoluble in water.

Found %: N 9.54; S 10.84. $C_{10}H_{12}O_6N_2S$. Calculated %: N 9.72; S 11.11.

2. The ethyl ester of α-N-(p-carbomethoxyaminobenzenesulfonyl)-d,l-alanine. A mixture of 8.15 g of α-N-(p-carbomethoxyaminobenzenesulfonyl)-d,l-alanine, 8 ml of concentrated sulfuric acid and 40 ml of alcohol was heated for 4 hours on a water bath at 80 – 84° with stirring. After cooling we isolated 7.6 g of material and a further 0.5 g by evaporating down the alcohol solution. The yield was 91%. The colorless needles with m.p. 144 – 144.5° were soluble in alcohol and insoluble in water, mineral acids and alkalis.

Found %: N 8.66; S 9.53. $C_{13}H_{18}O_6N_2S$. Calculated %: N 8.48; S 9.69.

3. The hydrazide of N-(p-aminobenzenesulfonyl)-glycine. A solution of 2.58 g of the ethyl ester of N-p-aminobenzenesulfonylglycine [9] and 1.25 ml of 80% hydrazine hydrate in 26 ml of anhydrous alcohol was heated on a boiling water bath for 4 hours. After evaporating the reaction mixture down in vacuum, the crystals obtained were washed with petroleum ether and anhydrous alcohol. After recrystallization from 50% alcohol the m.p. was 160°. The yield was 1.75 g (72%). The hydrazide was readily soluble in dilute hydrochloric acid, moderately in 50% alcohol and insoluble in ether, chloroform and ethyl acetate.

Found %: C 39.32; H 4.93; S 12.99. $C_8H_{12}O_3N_4S$. Calculated %: C 39.34; H 4.92; S 13.11.

4. The ethyl ester of α-N-(p-aminobenzenesulfonyl)-d,l-alanine. This was prepared from α-N-(p-aminobenzenesulfonyl)-d,l-alanine by esterification with ethyl alcohol in the presence of hydrogen chloride or sulfuric acid. The colorless, lustrous, crystalline substance with m.p. 110 – 111° was readily soluble in alcohol and dilute hydrochloric acid and insoluble in water. The yield was 10.44 g (85.3%).

Found %: N 10.36; S 11.92. $C_{11}H_{16}O_4N_2S$. Calculated %: N 10.29; S 11.72.

5. The amide of α-N-(p-aminobenzenesulfonyl)-d,l-alanine. A solution of the ethyl ester of α-N-(p-aminobenzenesulfonyl)-d,l-alanine in 30 ml of alcohol, saturated with ammonia while cooled, was kept at room temperature for 3 days. After evaporating the reaction mixture down in vacuum, the residue was recrystallized from 10 ml of water. The yield was 9.2 g (73.5 %). The amide obtained was colorless needles with m.p. 170.5–171.5°, which were soluble in alcohol and poorly soluble in water.

Found %: N 16.95; S 13.01. $C_9H_{13}O_3N_3S$. Calculated %: N 17.27; S 13.15.

The same amide was obtained from 2 g of the hydrazide of α-N-(p-aminobenzenesulfonyl)-d,l-alanine, 100 ml of 95% alcohol and 15 g of Raney nickel by stirring at the boiling point of the alcohol for 3 hours.

6. p-Hydroxy-m-methoxybenzalhydrazide of α-(p-aminobenzenesulfonamido)-propionic acid. 1 g of the hydrazide of α-N-(p-aminobenzenesulfonyl)-d,l-alanine in 20 ml of alcohol was heated up to 70° and a hot solution of 1 g of vanillin in 10 ml of alcohol was added. The mixture was left at room temperature for 2 days and then was heated on a boiling water bath for 4 hours. The precipitate melted at 172–175° after washing with alcohol and ether. The lustrous, yellow, crystalline material was poorly soluble in alcohol and insoluble in water and the usual organic solvents.

Found %: N 14.45. $C_{17}H_{20}O_5N_4S$. Calculated %: N 14.29.

7. N-(p-Acetylaminobenzenesulfonyl)-d,l-serine. To a solution of 5 g of d,l-serine in 60 ml of water, stirred at room temperature, was successively added 7 ml of 50% NaOH and 16 g of p-acetylaminobenzenesulfonyl chloride. The reaction medium was kept alkaline (to phenolphthalein) by adding 50% caustic soda (4 ml). After 1 hour, the solution was filtered and acidified with 20% hydrochloric acid (to Congo). We isolated 10.8 g of material. After recrystallization from 50% alcohol, the m.p. was 211–212° and it was insoluble in water and readily soluble in 50% alcohol.

Found %: C 43.83, 43.91; H 4.83, 4.81. $C_{11}H_{14}O_6N_2S$. Calculated %: C 43.71; H 4.63.

8. N-(p-Aminobenzenesulfonyl)-serine. A mixture of 7.3 g of N-(p-acetylaminobenzenesulfonyl)-d,l-serine and 75 ml of 15% hydrochloric acid was heated on a boiling water bath until there was complete solution. The solution was evaporated to dryness in vacuum and the residue was dissolved in 50 ml of water. After neutralization of the solution with sodium acetate we obtained 5.25 g (83.5%) of a substance. After 2 recrystallizations from 50% alcohol the m.p. was 212–212.5°; the colorless crystals were insoluble in ether and readily soluble in water and alcohol.

Found %: C 41.37, 41.30; H 4.47, 4.45; N 11.00, 10.64. $C_9H_{12}O_5N_2S$. Calculated %: C 41.54; H 4.61; N 10.77.

9. The ethyl ester of N-(p-aminobenzenesulfonyl)-serine. A solution of 30.2 g of N-(p-acetylaminobenzenesulfonyl)-d,l-serine in 350 ml of anhydrous alcohol was cooled and saturated with dry hydrogen chloride and on the following day was heated to boiling for 8 hours. The crystalline precipitate (24.5 g) was filtered off and washed with dry alcohol. The m.p. was 175–181°. By evaporation of the mother liquors we obtained a further 6.7 g of the substance. The yield was 31.2 g (96.25%). From the solution of the hydrochloride, by addition of caustic soda, we obtained a crystalline substance with m.p. 86–87°; it was readily soluble in alcohol and moderately in water.

Found %: C 45.72; H 5.40; N 9.76. $C_{11}H_{16}O_5N_2S$. Calculated %: C 45.83; H 5.56; N 9.72.

The same substance was prepared from N-(p-aminobenzenesulfonyl)-d,l-serine by esterification with anhydrous ethyl alcohol in the presence of hydrogen chloride.

10. The methyl ester of N (p-acetylaminobenzenesulfonyl)-d,l-serine A solution of 5.65 g of silver nitrate in 50 ml of water was quickly added with stirring to a solution of 10 g of N-(p-acetylaminobenzenesulfonyl)-d,l-serine and 1.9 g of potassium hydroxide in 90 ml of water. The mixture was protected from light and stirred for 15 minutes. The white precipitate of the silver salt was filtered off and washed with water and anhydrous alcohol. The yield was 11.7 g (87.5%).

To a suspension of 11.7 g of this silver salt in 220 ml of dry benzene, 8.5 ml (19 g) of methyliodide was gradually added over a period of 40 minutes with stirring and then the stirring was continued for 4 hours, while the mixture was protected from light. Then the reaction mixture was heated on a water bath at 25–60° for 2 hours and for 3 hours at the boiling point of the benzene. After cooling, 200 ml of methyl alcohol was added to the contents of the flask, the mixture was again heated to boiling and the silver iodide formed was then filtered off. The filtrate was evaporated down in vacuum and the crystalline precipitate obtained was recrystallized from 85 ml of methyl alcohol. We obtained 2.9 g of a colorless, crystalline substance. On cooling (–10°), we isolated a further 3.45 g from the mother liquor. The total yield was 70%. The m.p. was 164–165°. It was very readily soluble in methyl alcohol, insoluble in ether and benzene and also in solutions of bicarbonate and dilute hydrochloric acid.

Found %: C 45.40; H 5.04; N 8.53. $C_{12}H_{16}O_6N_2S$. Calculated %: C 45.57; H 5.06; N 8.86.

11. The methyl ester of α-(p-acetylaminobenzenesulfonamido)-β-chloropropionic acid. A mixture of 6 g of methyl ester of N-(p-acetylaminobenzenesulfonyl)-d,l-serine and 50 ml of freshly distilled thionyl chloride was gradually heated up to 65° over a period of 20 minutes with stirring and then for a further 5 minutes. Then the excess thionyl chloride was distilled off in vacuum without heating. On adding dry ether (100 ml) to the residue we obtained 4.72 g of a light yellow substance, which was soluble in methyl and ethyl alcohols and insoluble in ether and water; the m.p. was 130–136°. On standing in air the substance darkened. The yield was 74%.

Found %: Cl 10.89; N 8.21. $C_{12}H_{15}O_5N_2ClS$ Calculated %: Cl 10.61; N 8.37.

12. N-(p-Aminobenzenesulfonyl)-d,l-cysteine. A mixture of 1.67 g of the methyl ester of α-(p-acetylaminobenzenesulfonamido)-β-chloro-d,l-propionic acid and 2.4 g of potassium ethylxanthogenate in 5 ml of water was vigorously stirred at room temperature for 1 hour and then left for a day, after which it was acidified with 20% hydrochloric acid (to Congo). The precipitate was filtered off and washed with small portions of water. The xanthogenate derivative obtained (1.52 g) was dissolved in 12 ml of alcohol and the solution was treated with 10 ml of an aqueous solution of ammonia (25%). After three days standing at room temperature, the reaction mixture was carefully acidified to Congo with concentrated hydrochloric acid while cooled and then was evaporated down. The oily substance obtained, containing fine crystals, was heated with 10 ml of 15% hydrochloric acid until it completely dissolved and then the solution was treated with metallic zinc (7.5 g) for 0.5 hours. On evaporating down the solution in a stream of nitrogen, we obtained a clear, oily substance, which was dissolved in 3 ml of water and the solution was treated with sodium acetate until there was no acid reaction (Congo). In this way we isolated a white crystalline substance (1.12 g), which had m.p. 188–192° (with decomp.) after two recrystallizations from water (with $Na_2S_2O_4$ added). The yield was 0.73 g (53%). N-(p-Aminobenzenesulfonyl)-d,l-cysteine is a colorless, finely crystalline substance, which is soluble in water and insoluble in ether and chloroform. It forms a mercaptide with lead acetate as a white precipitate and gives a pale blue color with sodium nitroprusside.

Found %: N 10.27; S 23.34. $C_9H_{12}O_4N_2S_2$. Calculated %: N 10.14; S 23.18.

The same substance was obtained from d,l-cysteine.

To a solution of 2 g of d,l-cysteine, 0.4 g of hydrosulfite and 25 ml of water in a stream of nitrogen, were successively added 10 ml of 10% NaOH and 4.83 g of p-acetylaminobenzenesulfonyl chloride. The reaction medium was kept slightly alkaline by the addition of 10% caustic soda (11 ml). After 3 hours stirring in a stream of nitrogen, the alkaline solution was filtered and the filtrate was acidified to Congo with concentrated hydrochloric acid. The white precipitate obtained in this way (3.4 g) was heated with 40 ml of 15% hydrochloric acid on a boiling water bath for 1.5 hours. The acid solution was cooled to 50° and treated with metallic zinc (5 g) and then worked up as in the previous experiment. We obtained 1.85 g of a crystalline substance, which, after 2 recrystallizations from water, did not depress the melting point of N-(p-aminobenzenesulfonyl)-d,l-cysteine, synthesized by method 1 and melted at 188–191° (with decomp.).

13. The hydrochloride of N-(p-aminobenzenesulfonyl)-S-ethyl-d,l-cysteine. Ethyl mercaptan was passed into a solution prepared from 0.23 g of metallic sodium and 15 ml of anhydrous alcohol [10] and then a solution of 3.35 g of the methyl ester of α-(p-acetylaminobenzenesulfonamido)-β-chloro-d,l-propionic acid in 15 ml of anhydrous alcohol was added. The mixture was boiled for 2 hours. On evaporating down to dryness, we obtained an oily substance, which was heated with 20 ml of 15% hydrochloric acid on a boiling water bath until it completely dissolved (1.5 hours). The solution was evaporated in vacuum to 1/3 of the original volume; this precipitated a yellow crystalline substance which had m.p. 159–162° after 2 recrystallizations from 15% hydrochloric acid. It was very readily soluble in water and soluble in dilute hydrochloric acid and alkali. The substance obtained gave a negative reaction for a free mercapto group. The yield was 1.3 g (38.2%).

Found %: N 8.38; Cl 10.66. $C_{11}H_{16}O_4N_2S_2 \cdot HCl$. Calculated %: N 8.22; Cl 10.42.

The same substance was prepared from 1.38 g of N-(p-aminobenzenesulfonyl)-d,l-cysteine, 16 ml of 5% caustic soda, 8 ml of alcohol and 2.34 g of ethyl iodide by stirring in a stream of nitrogen for 14 hours.

14. The hydrochloride of N-(p-aminobenzenesulfonyl)-S-butyl-d,l-cysteine. 1.1 g of freshly distilled n-butyl mercaptan [11] was added to a solution of 0.23 g of metallic sodium in 20 ml of anhydrous alcohol. The reaction mixture was treated with a solution of 3.35 g of the methyl ester of α-(p-acetylaminobenzenesulfonamido)-β-chloro-d,l-propionic acid in 15 ml of anhydrous alcohol, as described for the preparation of the hydrochloride of N-(p-aminobenzenesulfonyl)-S-ethyl-d,l-cysteine. We obtained 1.58 g (43%) of the hydrochloride of N-(p-aminobenzenesulfonyl)-S-butyl-d,l-cysteine as colorless, lustrous, needle-like crystals with m.p. 148–152° (from 15% hydrochloric acid). The substance was readily soluble in water and poorly soluble in dilute hydrochloric acid. It gave a negative reaction for a mercapto group.

Found %: N 7.52; Cl 9.80. $C_{13}H_{20}O_4N_2S_2 \cdot HCl$. Calculated %: N 7.59; Cl 9.63.

The same substance was prepared from 0.83 g of N-(p-aminobenzenesulfonyl)-d,l-cysteine, 14 ml of 5% caustic soda solution, 7 ml of alcohol and 1.66 g of butyl iodide by stirring in a stream of nitrogen for 14 hours.

15. N-(p-Acetylaminobenzenesulfonyl)-S-ethyl-l-cysteine. To 125 ml of liquid ammonia was added successively 2.5 g of l-cysteine and 0.96 g of metallic sodium with vigorous stirring. After the disappearance of the blue color, the mixture was stirred with 4 ml (7.6 g) of ethyl iodide for 3 hours at room temperature; during this time the liquid ammonia evaporated. The white residue was dissolved in 100 ml of water and the solution was stirred for 2 hours, made alkaline to phenolphthalein and the unreacted ethyl iodide was extracted with ether. The aqueous solution was treated with 5.35 g of p-acetylaminobenzenesulfonyl chloride. After acidification, we obtained 2.8 g of a precipitate with m.p. 174–178°. The yield was 38.9% on the l-cysteine. After recrystallization from 60% alcohol, the colorless needles had m.p. 180–182° and were soluble in water and alcohol. They had $[\alpha]^{20}_{D}$ +8.0 (1% alcohol solution).

Found %: C 44.74; H 5.05; N 8.01. $C_{13}H_{18}O_5N_2S_2$. Calculated %: C 45.09; H 5.20; N 8.09.

16. N-(p-Aminobenzenesulfonyl)-S-ethyl-l-cysteine. N-(p-Acetylaminobenzenesulfonyl)-S-ethyl-l-cysteine (1.73 g) was hydrolyzed by heating with 30 ml of 15% hydrochloric acid on a boiling water bath for 1.5 hours. The solution was evaporated to dryness in vacuum. The oily residue was dissolved in 10 ml of water and the solution was neutralized with sodium acetate (to litmus). The precipitate had m.p. 152–153° after 2 crystallizations from water. It was readily soluble in water and alcohol. It had $[\alpha]^{20}_{D}$ −12.8 (1% solution in 2 N HCl).

Found %: C 43.35; H 5.14; N 9.29. $C_{11}H_{16}O_4N_2S_2$. Calculated %: C 43.42; H 5.26; N 9.21.

17. N-(p-Aminobenzenesulfonyl)-d,l-glutamic acid. A solution of 7.35 g of d,l-glutamic acid and 10 ml of 40% caustic soda in 75 ml of water was treated with 11.7 g of p-acetylaminobenzenesulfonyl chloride by the usual method. After acidification the solution was saturated with sodium chloride and extracted with ethyl acetate. Evaporation of the solution gave a crystalline residue, which was hydrolyzed by heating with 40 ml of 15% hydrochloric acid by the usual method. The material obtained was twice recrystallized to give lustrous, short needles with m.p. 175–175.5°, which were poorly soluble in water. The yield was 7.6 g (50.5% on the glutamic acid).

Found %: N 9.16; S 10.65. $C_{11}H_{14}O_6N_2S$. Calculated %: N 9.27; S 10.59.

18. N-(p-Aminobenzenesulfonyl)-d,l-norleucine. To a solution of 13.65 g of α-bromo-n-caproic acid in 45 ml of alcohol was added 21.1 g of the potassium salt of the sulfanilamide, prepared in 90% yield by mixing a hot solution of 17.2 g sulfanilamide in anhydrous alcohol with a 15% alcohol solution of 5.6 g of potassium hydroxide. The mixture was heated on a boiling water bath for 8 hours. The precipitate of potassium bromide was filtered off and the alcohol solution was evaporated to dryness in vacuum. The residue was treated with a 10% solution of soda and the solution was neutralized with acetic acid (litmus). The precipitate obtained, after recrystallization from water, was a colorless, fine crystalline substance with m.p. 164°, which was poorly soluble in cold water (1:100). The yield was 15.6 g (78%).

Found %: C 50.30; H 6.09; N 9.64. $C_{12}H_{18}O_4N_2S$. Calculated %: C 50.35; H 6.29; N 9.79.

The N-(p-aminobenzenesulfonyl)-d,l-norleucine obtained was recrystallized from 20% hydrochloric acid. Its hydrochloride was obtained as a colorless, coarsely crystalline substance with m.p. 172–176°.

Found %: N 8.46; Cl 10.93. $C_{12}H_{18}O_4N_2S \cdot HCl$. Calculated %: N 8.68; Cl 11.01.

19. N-(p-Acetylaminobenzenesulfonyl)-ε-leucine. From 10 g of cyclohexanone we obtained 11.3 g of its oxime, which was converted by Eck and Marvel's method [12] into ε-aminocaproic acid through caprolactam. The acid solution thus obtained was made alkaline with 40% sodium hydroxide (to phenolphthalein) and the solution was treated with p-acetylaminobenzenesulfonyl chloride (23.4 g) by Schotten-Baumann's method. The crystalline substance isolated was recrystallized from 50% alcohol. ε-(p-aminobenzenesulfonamido)-n-caproic acid was a colorless crystalline substance, which was readily soluble in alcohol, insoluble in water and had m.p. 146–147°. The yield was 23.6 g or 72%, calculated on the cyclohexanone.

Found %: C 51.31; H 6.10; N 8.44. $C_{14}H_{20}O_5N_2S$. Calculated %: C 51.22; H 6.09; N 8.54.

20. d,l-Leucine. 17.2 g of pure isovaleraldehyde (b.p. 90–92°) was gradually added with vigorous stirring over a period of 40 minutes to a solution prepared from 11 g of 95% sodium cyanide and 14 g of ammonium chloride in 50 ml of water. Then the mixture was heated at 60–63° for 1.5 hours with vigorous stirring. After cooling, the oily layer of the aminonitrile was separated from the aqueous layer and the latter was extracted with ether. Evaporation of the ether extract gave an oily substance, which was added to the aminonitrile isolated. We obtained 22.2 g of technical α-aminoisocapronitrile as a dark oil.

70 ml of concentrated hydrochloric acid was added to the aminonitrile obtained with energetic stirring. The reaction mixture was carefully heated to 90–93°; at this it effervesced vigorously. After 10 hours heating the aminonitrile completely dissolved. The solution was filtered to remove the tar formed and evaporated to dryness in vacuum. To remove the excess hydrogen chloride from the residue, water was added and distilled off several times. The white crystalline residue (35.5 g) was a mixture of the hydrochloride of d,l-leucine and ammonium chloride and was recrystallized from 50 ml of water by heating. We obtained 8.6 g of the hydrochloride of d,l-leucine as a colorless crystalline substance with m.p. 230° (from 20% hydrochloric acid). By neutralizing an aqueous solution of the amino acid hydrochloride with bicarbonate, we isolated 3.12 g of d,l-leucine, which after recrystallization from water (100 ml) formed colorless, lustrous plates (2.82 g) with m.p. 268–270°; it did not depress the melting point (267–269°) of d,l-leucine. The overall yield was 36.5%, calculated on the aldehyde.

SUMMARY

1. We prepared a series of previously unknown sulfanyl derivatives of the following natural amino acids: glycine, alanine, phenylalanine, serine, cysteine, cystine, dimethylcysteine, methionine, leucine, norleucine, ε-leucine, glutamic acid, proline and tryptophan, their esters, hydrazides and hydrazones.

2. Besides forming esters the N-acetyl group was saponified in the esterification of N-(p-acetylaminobenzenesulfonyl)-amino acids. The esters of N-(p-acetylaminobenzenesulfonyl)-amino acids were obtained by treating their silver salts with alkyl iodides.

3. Using N-(p-aminobenzenesulfonyl)-alanine as an example, it was shown that the hydrazides of N-(p-aminobenzenesulfonyl)-amino acids may be converted into the corresponding amides by treatment with a nickel catalyst.

4. N-(p-aminobenzenesulfonyl)-cysteine and its S-alkylated derivatives were synthesized from the sulfanyl derivative of serine.

5. It was shown that no migration of the sulfanilyl group from nitrogen to oxygen took place in N-(p-aminobenzenesulfonyl)-serine when it was treated with acids.

6. Sulfanyl derivatives of amino acids containing a free sulfhydryl group were synthesized.

7. A new way of synthesizing N-(p-aminobenzenesulfonyl)-amino acids was developed which consisted of reacting the potassium salt of sulfanilamide with the halo acids.

8. No materials with high anti-bacterial activity were found among the preparations synthesized.

LITERATURE CITED

[1] M. L. Crossley, E. N. Northey, M. E. Hultanist, J. Am. Chem.Soc., 60, 2217 (1938).

[2] Kamlet, Am. Chem. Soc. Meeting at Rochester, N. Y. Sept. 19; Kollof., J. Am. Chem. Soc., 60, 950 (1938); V. A. Mikhalev, and A. P. Skoldinov, J. Appl. Chem. 19, 1837 (1946).

[3] M. N. Shchukina and Yuan Chen-e, J. Gen. Chem. 24, 687 (1954).

[4] M. V. Rubtsov and V. G. Klimko, J. Gen. Chem. 16, 1865 (1945).

[5] T. Wagner-Jauregg u. W. H. Wagner, Z. Naturforsch., 1, 229 (1946).

[6] F. P. Mazza, C. Migliardi, Atti Linc., 6, 28, 152 (1938).

[7] T. Dewing, W. H. Gray, J. Chem. Soc., 1942, 239; K. Ganapati, Proceed. Indian Acad. Sci., 11A, 298 (1940).

[8] S. Archer, T. O. Hoppe, T. R. Lewis, J. Am pharm. Assoc., 40, 193 (1951).

[9] M. L. Crossley, E. U. Northey, Hullquist, J. Am. Chem. Soc., 62, 532 (1940).

[10] E. Brand, F. C. Brand, Org. Synthesis 22, 59.

[11] T. W. Kimball, E. E. Reid, J. Am Chem. Soc., 38, 2757 (1916).

[12] J. C. Eck, C. S. Marvel, Marvel, J. Biol. Chem., 106, 387 (1934).

Received March 24, 1956

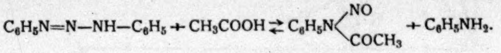
S. Ordzhonikidze All-Union Institute for the
Scientific Investigation of Chemical Pharmaceutics

INVESTIGATION OF THE PROCESS OF POLYMERIZATION OF STYRENE UNDER THE INFLUENCE OF DIAZOAMINO COMPOUNDS AND ACTIVATORS

P. A. Vinogradov

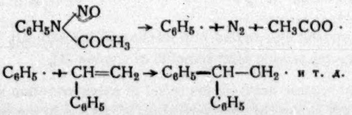
B. V. Byzov [1] was the first to employ diazoamino compounds as initiators of polymerization. He effected the polymerization of isoprene and butadiene in presence of diazoamino compounds in the condensed phase and the process went with extreme slowness at a sufficiently high temperature (100-150°).

The present investigation established that the rate of polymerization of unsaturated compounds in the condensed phase in presence of diazoamino compounds is considerably increased under the influence of organic acids and their anhydrides. In our opinion, this effect is due to acceleration of the breakdown of the diazoamino compounds which is accompanied by formation of intermediate compounds – nitrosoacyl-arylamines. For example, under the influence of acetic acid, diazoaminobenzene can break down with formation of nitrosoacetylanilide:



$$C_6H_5N{=}N{-}NH{-}C_6H_5 + CH_3COOH \rightleftarrows C_6H_5N\left\langle\begin{matrix}NO\\ COCH_3\end{matrix}\right. + C_6H_5NH_2.$$

The latter is unstable and decomposes with formation of free radicals which initiate polymerization [2]:



$$C_6H_5N\left\langle\begin{matrix}NO\\ COCH_3\end{matrix}\right. \rightarrow C_6H_5\cdot + N_2 + CH_3COO\cdot$$

$$C_6H_5\cdot + \underset{\displaystyle C_6H_5}{\underset{|}{CH}}{=}CH_2 \rightarrow C_6H_5{-}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}{-}CH_2\cdot \text{ и т. д.}$$

EXPERIMENTAL

Influence of organic acids and their anhydrides on the rate of polymerization. The monomer selected for the experiments was styrene, d_4^{20} 0.9055, styrene content 99.9%. It was stabilized with hydroquinone. Prior to each experiment the hydroquinone was removed by washing with alkali solution and the styrene was then dried with calcium chloride and used immediately after distillation. Diazoaminobenzene (DAB) was obtained by recrystallization of the technical product from ethyl alcohol. The purified product contained 98-99% diazoaminobenzene. Organic acids, apart from formic and oleic acids, were used in the form of pure preparations. Formic acid (technical) was concentrated by distillation with phosphorus pentoxide [3]. Oleic acid was isolated by vacuum distillation of the technical material. Acetic anhydride was used after fractional distillation of the reagent grade.

Polymerization of styrene was effected in 10-12 ml ampoules. Diazoaminobenzene (2wt.-%) was added to the styrene before the experiment. Organic acid or anhydride was added in varying proportions. All the necessary operations were conducted in a nitrogen atmosphere. The sealed ampoules containing the reaction mixtures were heated in an oil thermostat at 70 ± 0.2°. At definite intervals of time the ampoules were taken

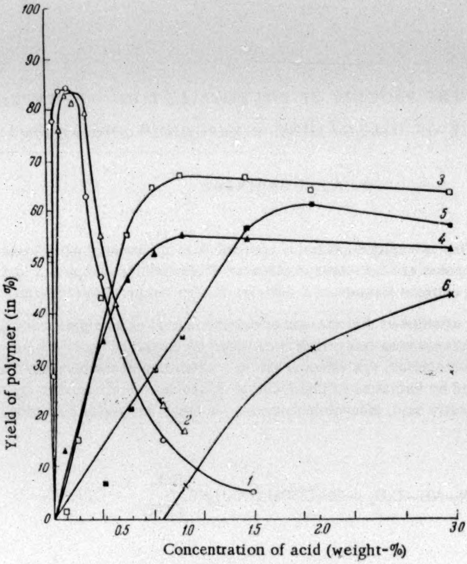


Fig. 1. Influence of acids on the speed of polymerization. 1) monochloroacetic acid; 2) formic acid; 3) acetic acid; 4) benzoic acid; 5) butyric acid; 6) oleic acid.

out consecutively from the thermostat and cooled in a mixture of ice and salt. The amount of polymer formed was determined by weighing the dry residue after removal of styrene [1].

The influence of different organic acids on the speed of polymerization was investigated. The experimental data (Fig. 1) show that the process of polymerization of styrene in the condensed phase under the influence of diazoaminobenzene is considerably accelerated in presence of organic acids. The ability to accelerate polymerization of the diazoaminobenzene-initiated process is not a specific property of individual acids but is a general property common to all acids soluble in hydrocarbons.

The influence of acetic and maleic anhydrides was examined. The data of Fig. 2 show that hydrocarbon-soluble anhydrides of organic acids likewise accelerate the process of polymerization of styrene in the condensed phase under the influence of diazoaminobenzene.

A similar influence of organic acids on the speed of polymerization of styrene is observed in presence of o,o'-dimethyldiazoaminobenzene and of p,p'-dimethyldiazoaminobenzene (Table 1).

o,o'-Dimethyldiazoaminobenzene and p,p'-dimethyldiazoaminobenzene were synthesized in the usual manner by diazotization and simultaneous coupling of the respective toluidines [5].

Kinetics of polymerization and kinetics of breakdown of diazoaminobenzene.

One of the factors known to govern the velocity of polymerization is the rate of breakdown of the initiator [4, 6]. In our investigation we studied the influence of organic acids on the rate of breakdown of diazoaminobenzene during the polymerization of styrene. For this purpose we instituted kinetic experiments in which we determined, apart from the polymer yield, the amount of nitrogen released during polymerization and the content of undecomposed diazoaminobenzene.

The volume of nitrogen released was measured with a buret in the course of the entire experiment. The amount of diazoaminobenzene decomposed was calculated from the volume of nitrogen found. The diazoaminobenzene in the styrene and in the polymerizing mixture was determined by the method based on its breakdown by hydrochloric acid [7]. Data characterizing the accuracy of determination of diazoaminobenzene in the polymer solution are presented in Table 2.

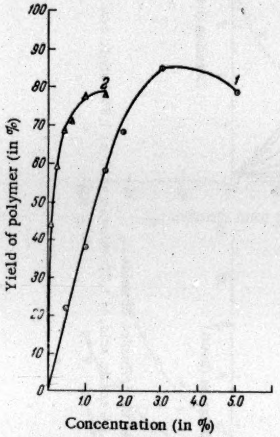


Fig. 2. Influence of anhydrides of organic acids on the speed of polymerization.
1) Acetic anhydride; 2) maleic anhydride.

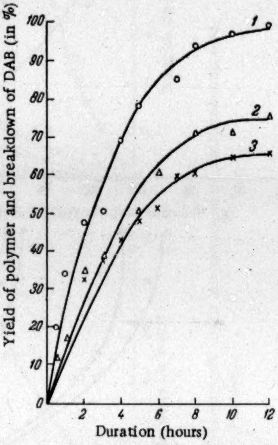


Fig. 3. Rate of polymerization and breakdown of diazoaminobenzene (DAB).
1) Yield of polymer; 2) total breakdown of DAB; 3) breakdown of DAB (from nitrogen released).

Experimental results for the speed of styrene polymerization and of diazoaminobenzene breakdown during the reaction are plotted in Fig. 3 which relates to results obtained in presence of 0.15% monochloroacetic acid. An interesting fact that emerges from the results is that during polymerization in presence of organic acids, the diazoaminobenzene undergoes transformation both with and without liberation of nitrogen.

Kinetic data for the influence of different organic acids on the speed of polymerization and on the breakdown of diazoaminobenzene are presented in Fig. 4. The data clearly establish a relation between speed of polymerization and breakdown of diazoaminobenzene, rise of speed of polymerization being accompanied by acceleration of decomposition of diazoaminobenzene. We can also observe a relation between speed of polymerization and breakdown of diazoaminobenzene on the one hand and acid strength on the other hand. The stronger the acid the higher the speed of polymerization and the greater the decomposition of diazoaminobenzene as judged by the total concentration of the latter and by the volume of nitrogen released. The results enable the organic acids used in the investigation to be arranged in the following order of activity in the polymerization process: monochloroacetic acid > formic > acetic > benzoic > butyric > oleic.

Results of experiments on polymerization of styrene and breakdown of diazoaminobenzene in presence of various concentrations of monochloroacetic acid are plotted in Fig. 5. We can see that increasing concentration of acid up to a certain limit (about 0.3%) is accompanied by a steady rise in velocity of polymerization

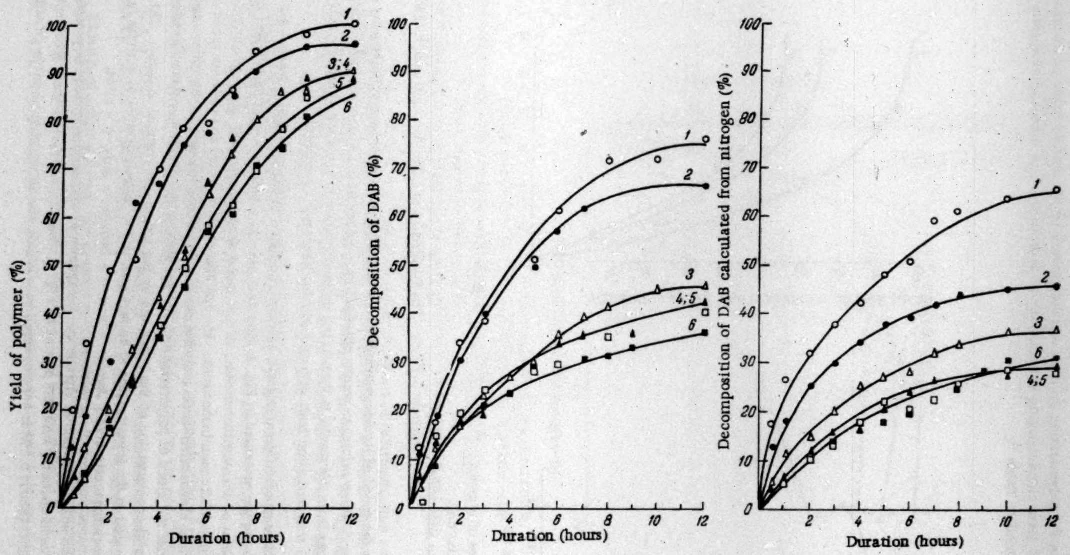


Fig. 4. Speed of polymerization and breakdown of DAB under the influence of acids.
1) 0.15% monochloroacetic acid; 2) 0.15% formic acid; 3) 1.0% acetic acid; 4) 1.2% benzoic acid; 5) 1.8% butyric acid; 6) 5% oleic acid.

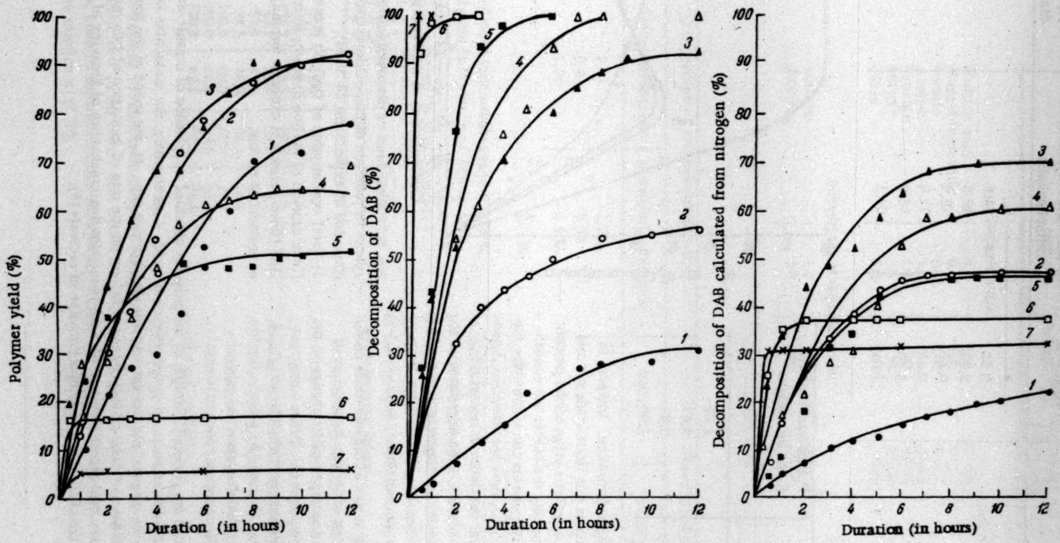


Fig. 5. Rate of polymerization and of breakdown of diazoaminobenzene (DAB) in presence of monochloroacetic acid. 1) 0.028%; 2) 0.056%; 3) 0.15%; 4) 0.29%; 5) 0.4%; 6) 0.74%; 7) 1.49%.

TABLE 1

Polymerization of Styrene in Presence of Different Diazoamino Compounds and Organic Acids (Concentration of initiator 2 weight-% on the styrene, temperature of experiments 70°, duration 6 hours)

Name of acid	Optimum acid concentration (weight-%)	Yield of polymer (weight-%) with polymerization initiator	
		o,o'-dimethyldiazoaminobenzene	p,p'-dimethyldiazoaminobenzene
Without acid	0	0	0
Monochloroacetic Acid	0.02	94.6	87.2
Formic	0.05	86.3	85.2
Acetic	0.40	79.4	71.4
Benzoic	0.40	77.0	63.4
Butyric	0.40	76.3	60.7
Oleic	1.0	69.1	49.7

TABLE 2

Diazoaminobenzene introduced into solution of polystyrene in xylene (weight-%)	Diazoaminobenzene found by analysis (weight-%)
0.21	0.22
0.50	0.47
1.01	0.99
2.03	1.99

and in velocity of nitrogen formation. Increase in concentration of acid up to this limit leads to cessation of the reaction at a definite stage of the process. This occurs the more quickly the higher the concentration of acid. A similar correlation is found for the formation of nitrogen. The total breakdown of diazoaminobenzene, however, continues to rise with increasing concentration of acid. The experimental results permit us to conclude that stoppage of the polymerization reaction coincides with complete disappearance of the diazoaminobenzene.

The accelerating action of organic acids on the process of polymerization of styrene in presence of diazoaminobenzene is accompanied by change in the molecular weight of the polymer. Table 3 contains data characterizing the average molecular weight of specimens of polystyrene obtained by polymerization in presence of 2% diazoaminobenzene and organic acids and anhydrides (in optimum concentrations).

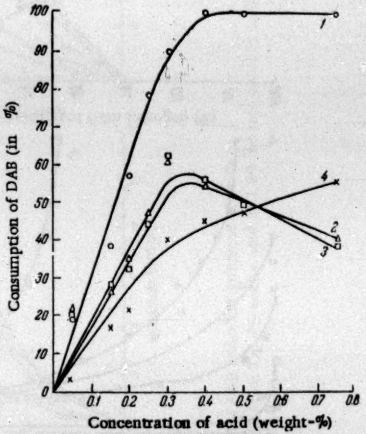


Fig. 6. Breakdown of diazoaminobenzene (DAB) in xylene in presence of monochloroacetic acid. (Duration of experiment 15 hours).
1) Total consumption of DAB; 2) breakdown of DAB (from amount of aniline formed); 3) breakdown of DAB (from volume of nitrogen formed); 4) formation of aminoazobenzene.

The data show that the molecular weight of the polymer obtained in presence of organic acid is considerably lower than that of polymer obtained in the absence of acid. Consequently, the molecular weight of the polymer changes with the speed of the process. As was shown above (Fig. 4), the speed of the process depends upon the speed of breakdown of diazoaminobenzene or in turn on the rate of formation of free radicals. Consequently, the results obtained are in harmony with the recombination mechanism of breaking of the molecular chain or of rupture of the chain due to disproportionation of radicals [8].

TABLE 3

Molecular Weight of Polystyrene
(Polymerization temperature 70°)

Name of activator	Activator concentration (%)	Yield of polystyrene (weight-%)	Average molecular weight of polystyrene
Organic acids			
Without acid	0	100	106900
Monochloroacetic	0.15	100	17000
Formic	0.15	100	17800
Acetic	1.0	98.0	25300
Benzoic	1.2	97.5	25800
Butyric	1.8	94.0	27400
Oleic	5.0	100	33100
Anhydrides of organic acids			
Maleic	1.0	94.0	19800
Acetic	3.0	100	19200

TABLE 4

Composition of mixture (weight-%)			Determined (weight-%)	
Aniline	Aminoazobenzene	Diazoaminobenzene	Aniline	Aminoazobenzene
0.37	0.43	1.02	0.38	0.41
0.58	0.37	0.95	0.53	0.33
0.21	1.00	0.98	0.32	0.94

TABLE 5

Decomposition of Diazoaminobenzene (DAB) in Xylene Solution in Presence of Acetic Acid

Concentration of acid (weight-%)	Total fall in amount of DAB (in %)	Found (in % of original amount of DAB)		
		aniline	nitrogen	aminoazobenzene
1.0	23.3	18.4	19.0	5.3
2.0	26,0	19.6	18.8	5.9
3.0	31.5	25.5	22.2	7.3
4.0	43.5	29.9	33.2	8.7
5.0	57.0	47.5	32.7	10.7
7.0	88.3	56.0	54.3	28.9
10.0	100.0	60.3	60.6	33.6
12.0	100.0	66.2	63.0	33.5
15.0	100.0	62.5	54.3	38.4

Determination of composition of products of breakdown of diazoaminobenzene. B. A. Dolgoplosk et al. [9] studied the thermal breakdown of diazoaminobenzene in butylbenzene and characterized it only by the rate of liberation of nitrogen during the reaction. There are no other literature data for the composition of the products of breakdown of diazoaminobenzene in a hydrocarbon medium.

Under our polymerization conditions, substances, apart from nitrogen, likely to be formed during breakdown of diazoaminobenzene are aniline and aminoazobenzene. Due to the analytical difficulties of determination of these compounds in the polymer or in polymer solution, the breakdown of diazoaminobenzene was effected in xylene solution, and the products of breakdown were studied.

For determination of aniline, the latter was separated from the xylene solution in the form of the hydrochloride by washing 10 g of the mixture at 0° with dilute hydrochloric acid (4 ml chem. pure hydrochloric acid in 100 ml water). The aniline in the hydrochloric acid solution, after its separation from the xylene solution, was determined by diazo titration with 0.1 N sodium nitrite solution at 0° [7].

Aminoazobenzene was determined by reduction with a hydrochloric acid solution of tin chloride by the method of Limpricht [7]. Prior to reduction of the aminoazobenzene, the reagent acid, containing a weighed sample (10 g) of material and 15 ml hydrochloric acid, was heated on a boiling water bath until the diazoaminobenzene was completely decomposed. A standard solution of tin chloride was then run into the flask in a stream of carbon dioxide, and the flask was again heated for $3^1/_2$ hours. After cooling, the excess of tin chloride was back-titrated with 0.1 N potassium bichromate in presence of potassium iodide, using starch as indicator. Tests of these procedures with artificial mixtures of aniline and aminoazobenzene gave sufficiently accurate results (Table 4).

Decomposition of diazoaminobenzene in xylene solution was carried out in presence of monochloroacetic acid (various concentrations). The experiments were effected in a thermostat at 70° for 15 hours. In all experiments the concentration of diazoaminobenzene was 2%. Diazoaminobenzene, aniline and aminoazobenzene were determined in xylene solution containing the products of breakdown of diazoaminobenzene. In addition, the volume of nitrogen released during breakdown was measured during each experiment. Diphenylamine was not quantitatively determined since qualitative tests [7] were negative. Results of determination of the products of breakdown of diazoaminobenzene under the action of monochloroacetic acid are plotted in Fig. 6, and those in presence of acetic acid are presented in Table 5.

The results obtained reveal the following regular features of the breakdown: 1) the rate of breakdown of diazoaminobenzene is proportional to the acid concentration; 2) the rate of rearrangement of diazoaminobenzene into aminoazobenzene is proportional to the concentration of acid; 3) aniline and nitrogen are formed in substantially equal amounts, and the curve of their formation contains a maximum.

If we assume that the process of rearrangement of diazoaminobenzene into aminoazobenzene is not related to the initiation of the polymerization process, then the speed of polymerization is evidently governed by the speed of breakdown of diazoaminobenzene which is bound up with the formation of aniline and nitrogen. This also, most probably, governs the difference in activities of different acids during polymerization.

In conclusion I extend profound thanks to B. A. Dolgoplosk, S. S. Medvedev and E. A. Shilov for valuable advice and interest during the work.

SUMMARY

1. An activating action of organic acids and anhydrides on the process of polymerization of unsaturated compounds in the condensed phase under the influence of diazoamino compounds was established.

2. The kinetics of polymerization of styrene and the kinetics of breakdown of diazoaminobenzene under the influence of organic acids were studied.

3. The composition of the products of decomposition of diazoaminobenzene in xylene solution was determined.

LITERATURE CITED

[1] B. V. Byzov, J. Appl. Chem. (USSR) 6, 1074 (1933).

[2] D. Hey, and W. Waters, Chem. Revs. 21, 1, 169 (1937); A. Blomquist, J. Jonson, and H. Skyes, J. Am. Chem. Soc. 65, 2446 (1943).

[3] A. I. Gulyaeva, V. F. Polikarpova and Z. K. Remiz, Analysis of products in manufacture of butadiene from ethyl alcohol by the method of S. V. Lebedev (State Chemical Press, 1950), 120.

[4] S. Kamenskaya and S. Medvedev, J. Phys. Chem. 14, 922 (1940).

[5] Beilst. 14, 703 (1940).

[6] S. Medvedev, O. Koritskaya and E. Alekseeva, J. Phys. Chem. 17, 391 (1943); T. I. Yurzhenko, G. N. Gromova and V. B. Khaitser, J. Gen. Chem. 16, 1505 (1946); T. I. Yurzhenko, Chemistry and physical chemistry of high-molecular compounds (Academy of Sciences Press, 1952) 51.

[7] H. Meyer, Analysis and determination of structure of organic compounds, (United Sci - Tech Press The People's Commissariat of Heavy Industry, Kharkov, Kiev, 1935), 558.

[8] P. Flory, J. Am. Chem. Soc. 59, 241 (1937).

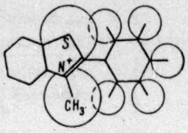
[9] B. A. Dolgoplosk, P. G. Ugryumov and V. A. Krol, Proc. Acad. Sci. USSR 96, 757 (1954).

Received October 19, 1955

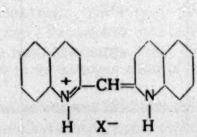
STERIC HINDRANCE IN QUATERNARY SALTS OF 2-ARYLBENZOTHIAZOLES AND 2-ARYLBENZOSELENAZOLES

A. I. Kiprianov and V. A. Shrubovich

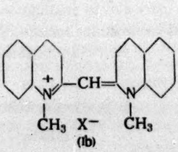
No considerable steric hindrance to a planar state of the molecules should occur in the case of 2-phenylbenzothiazole or diphenyl [1]. In the cation of 2-phenylbenzothiazole methiodide, however, this type of hindrance arises as we see from the drawing.* On comparing the absorption spectra of salts of 2-arylbenzothiazoles, e.g., sulfates, with the absorption spectra of their quaternary salts, we can detect (qualitatively at least) a distortion of the coplanarity of the rings in the quaternary salts.



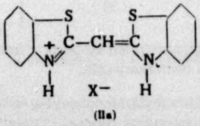
The absorption maxima of solutions of salts of organic bases and their quaternary salts are known to coincide or to differ only slightly from one another; in the latter event, the absorption maximum of the quaternary salt is shifted in the long-wave direction. Thus, for example, the absorption maxima of quinoline sulfate and methiodide coincide in alcohol (313 m μ), and the absorption maxima of solutions of monomethylanilines (Ia) and (Ib) (523 mμ [3]) and (IIa) and (IIb) (425 mμ [4]) coincide. The absorption maximum of pyridine methiodide in alcohol (258 mμ) is nearer the long-wave region than the absorption maximum of pyridine sulfate (254 mμ). The same is true of alcoholic solutions of 2-methylbenzothiazole methiodide (265 mμ) and its sulfate (261 mμ). Only very rarely is the absorption maximum of the sulfate of a base nearer the red end of the spectrum than the absorption maximum of the methiodide or ethiodide.



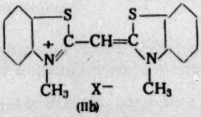
(Ia)



(Ib)



(IIa)



(IIb)

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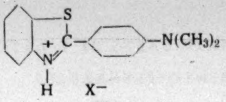
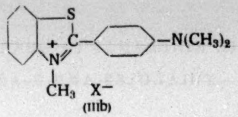
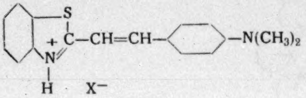
[*] Concerning the atomic radii assumed in the diagram, see [2].

A. I. Kiprianov and I. K. Ushenko [5], also Brooker et al. [6], showed that the shift of the absorption maximum towards the short waves in dyes of unsymmetrical structure may be the result of distortion of the coplanarity of the rings. Such a phenomenon is indeed observed, as we have now shown, in quaternary salts of 2-p-dimethylaminophenylbenzothiazole (IIIa) and (IIIb):


(IIIa)


(IIIb)

In the cation of salt (IIIa) the benzene and benzothiazole rings are coplanar, while in the cation of salt (IIIb) the coplanarity is distorted. Consequently the relative positions of the absorption maxima of (IIIa) and (IIIb) deviate from the general rule, that of (IIIb) being displaced not towards the long-wave region of the spectrum but towards the short-wave region. The usual rule is followed in the vinylene homologs (IVa) and (IVb) of salts (IIIa) and (IIIb), since the coplanarity of the rings is not hindered.


(IVa)

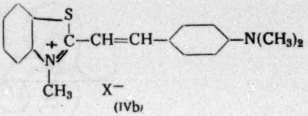

(IVb)

Table 1 contains the results of determinations made with salts of 2-p-dimethylaminophenylbenzothiazole, 2-p-diethylaminophenyl-6-methylbenzothiazole and 2-p-dimethylaminostyrylbenzothiazole in alcoholic solutions.

TABLE 1

Name of Salt		λ_{max} (in m μ)	Displacement of λ_{max} (in mμ)
2-p-Dimethylaminophenylbenzothiazole	sulfate	432	–
	methiodide	420	–12
	ethiodide	423	– 9
2-p-Diethylaminophenyl-6-methylbenzothiazole	sulfate	435	–
	ethiodide	427	– 8
2-p-Dimethylaminostyrylbenzothiazole	sulfate	510	–
	ethiodide	530	+20

We see that the hypsochromic shift of the absorption maximum on passing from salt solution to quaternary salt solution can serve as a criterion of steric hindrance in a quaternary salt.

Similar observations were made with salts of 2-p-dimethylaminophenyl-α-naphthothiazole, as well as of 2-p-dimethylaminophenylbenzoselenazole and the corresponding styrenes (Table 2).

TABLE 2

Name of Salt		λ_{max} (in m μ)	Shift of λ_{max} (in m μ)
2-p-Dimethylaminophenyl-α-naphthothiazole	sulfate	445	–
	ethiodide	430	–15
2-p-Dimethylaminostyryl-α-naphthothiazole	sulfate	517	–
	methiodide	537	+20
2-p-Dimethylaminophenylbenzoselenazole	sulfate	439	–
	ethoperchlorate	430	– 9
2-p-Dimethylaminostyrylbenzoselenazole	sulfate	516	–
	ethiodide	537	+21

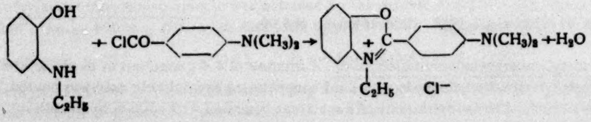
TABLE 3

Name of Salt		λ_{max} (in m μ)	Shift of λ_{max} (in m μ)
2-p-Dimethylaminophenylbenzoxazole	sulfate	397	–
	ethoperchlorate	400	+ 3
2-p-Dimethylaminostyrylbenzoxazole	sulfate	483	–
	methiodide	495	+12

The radius of the selenium atom (1.17 A) only differs slightly from that of the sulfur atom (1.04 A) [7], so that the steric hindrance developed in quaternary salts of 2-arylbenzothiazoles also occurs in quaternary salts of 2-arylbenzoselenazoles. Good confirmation of the hypothesis that steric hindrance is here involved is provided by the fact that the absorption maximum of benzoxazole sulfate is at a shorter wave-length than the maximum of its quaternary salt. The radius of the oxygen atom (0.66 A) is very much smaller than the radii of sulfur and selenium, so that there is no deviation from coplanarity in the quaternary salts of 2-arylbenzoxazoles. The absorption maxima of salts of 2-p-dimethylaminophenylbenzoxazole and of the corresponding styryl compound are given in Table 3.

No difficulties were presented by the synthesis of 2-p-dialkylaminophenyl derivatives of benzothiazole, 6-methylbenzothiazole, α-naphthothiazole and benzoselenazole or of their quaternary salts. Some of these compounds are described in the literature. Difficulties arose in the preparation of the quaternary salt of 2-p-dimethylaminophenylbenzoxazole. The ethyl-p-toluenesulfonate of this base, obtained by the action of ethyl-p-toluenesulfonate on it, had an absorption maximum in alcohol solution at 300 mμ, which nearly coincides with the maximum of the base itself (295 mμ). Thus, due to the weakness of the basic properties of benzoxazole, the ethyl radical is linked not to the nitrogen atom of benzoxazole but to the dimethylamino group.

Another route had to be adopted to obtain the quaternary salt of interest to us. We condensed N-ethyl-o-aminophenol with p-dimethylaminobenzoyl chloride in accordance with the equation:



The quaternary salt, isolated by us in the pure state as the perchlorate with an absorption maximum at 400 mμ, was very unstable and broke down fairly rapidly even in alcoholic solution.

It should also be noted that the method of preparation of the acid chloride of p-dimethylaminobenzoic acid by treatment with phosphorus pentachloride, described by Decombe [8], was tried and found unsuitable. We also obtained the pure acid chloride in good yield by the action of oxalyl chloride on the potassium salt of dimethylaminobenzoic acid by the method recently proposed for the preparation of nicotinic acid chloride [9].

EXPERIMENTAL

2-p-Dimethylaminophenylbenzothiazole. A mixture of 7.2 g o-aminothiophenol and 8.3 g p-dimethylaminobenzaldehyde was heated 3 hours at 100°. The solidifying mass was twice recrystallized from alcohol. Yield 3.3 g (23%) of yellowish needles, m.p. 172°, λ_{max} 362 mμ. The alcoholic solutions have a strong blue fluorescence. Bogert and Taylor [10] obtained this base by heating p-dimethylaminobenzaldehyde with o,o-diaminodiphenyl disulfide at 160-170°; they report m.p. 174-175°.

The methiodide was obtained by heating the base with methyl iodide in benzene solution for 5 hours at 130-140°; bright-yellow needles with m.p. 220° with decomposition after recrystallization from water (the literature reports [10]: 223-224° with decomp.); λ_{max} 420 mμ.

The ethiodide was obtained from the base and the ethyl ester of p-toluenesulfonic acid in nitrobenzene by heating for 2 hours at 150°. The nitrobenzene was distilled off with steam and the aqueous solution of the salt was treated with potassium iodide. After recrystallization from water the product formed yellow tablets with m.p. 176°, λ_{max} 423 mμ.

Found %: N 6.77. $C_{17}H_{19}N_2SI$. Calculated %: N 6.83.

6-Methyl-2-p-diethylaminophenylbenzothiazole was obtained by the action of diethyl sulfate and sodium carbonate on dehydrothiotoluidine [11]. Pale-yellow crystals, m.p. 116°, λ_{max} 364 mμ; blue fluorescence in an alcoholic solution.

The ethiodide was obtained by heating the base with the ethyl ester of p-toluenesulfonic acid for 2 hours at 150° and precipitation of the aqueous solution with potassium iodide. Recrystallization from alcohol gave yellow needles, m.p. 140°, λ_{max} 427 mμ.

Found %: N 6.05, 6.15. $C_{20}H_{25}N_2SI$. Calculated %: N 6.19.

2-p-Dimethylaminophenyl-α-naphthothiazole. 6 g unpurified thiazonium chloride, obtained from β-naphthylamine hydrochloride and S_2Cl_2 in glacial acetic acid [12], was suspended in alcohol and heated to the boil with an alcoholic solution of 4 g potassium hydroxide. After filtration, 3.6 g p-dimethylaminobenzaldehyde was added and the mixture refluxed $1^1/_2$ hours. After half of the alcohol had been distilled off, yellowish crystals came down. Yield 0.63 g, m.p. 174°, λ_{max} 370 mμ. The alcoholic solutions have a blue fluorescence.

Found %: N 9.34, 9.34. $C_{19}H_{16}N_2S$. Calculated %: N 9.21.

The ethiodide was prepared by heating a mixture of the base and ethyl p-toluenesulfonate for $4^1/_2$ hours at 150° and precipitating the aqueous solution of the salt with potassium iodide. Crystallization from alcohol gave yellow-orange needles, m.p. 165-166°, λ_{max} 430 mμ.

Found %: N 6.10. $C_{21}H_{21}N_2SI$. Calculated %: N 6.09.

2-p-Dimethylaminophenylbenzoselenazole. A mixture of 4.4 g zinc salt of o-aminoselenophenol [13] and 3.2 g p-dimethylaminobenzaldehyde with 2 ml concentrated hydrochloric acid was heated 1 hour at 100° and 10 minutes at 130°. The brownish semisolid mass was triturated with sodium hydroxide solution and then with hydrochloric acid. Since the purity was inadequate after recrystallization from alcohol, the product was dissolved in chloroform and chromatographed on alumina. The yellow chloroform solution of the base was evaporated and the solid residue recrystallized from a mixture of chloroform and alcohol to give about 1 g small colorless needles with m.p. 178°, λ_{max} 364 mμ.

Found %: N 9.41, 9.49. $C_{15}H_{14}N_2Se$. Calculated % N 9.30.

The ethoperchlorate was prepared from the base and diethyl sulfate by heating at 120° for 1 hour and precipitating the aqueous solution of the salt with sodium perchlorate. Crystallization from alcohol gave yellow needles, m.p. 170° (with decomp.), λ_{max} 430 mμ.

Found %: N 6.22, 6.37. $C_{17}H_{19}O_4N_2ClSe$. Calculated %: N 6.51.

2-p-Dimethylaminophenylbenzoxazole was obtained by the action of lead tetraacetate on the anil formed from o-aminophenol and p-dimethylaminobenzaldehyde [14]. M.p. 182-183°, λ_{max} 295 mμ.

[4-(Benzoxazolyl-2')-phenyl] - dimethylethylammonium tosylate was obtained by heating 2-p-dimethylaminophenylbenzoxazole with ethyl p-toluenesulfonate (3 hours at 130°). The salt was recrystallized from chloroform. Colorless needles, m.p. 190-191°, λ_{max} 300 mμ.

Found %: N 6.36; S 7.32, 7.45. $C_{24}H_{26}O_4N_2S$. Calculated %: N 6.48; S 7.41.

p-Dimethylaminobenzoyl chloride. p-Dimethylaminobenzoic acid with m.p. 235-238° was obtained from p-dimethylaminobenzaldehyde by potassium hydroxide fusion as described by Decombe [8]. All our attempts to apply this author's method of preparation of dimethylaminobenzoyl chloride (action of phosphorus pentachloride on the acid in carbon bisulfide with pyridine present) only led to high-melting products. Decombe evidently also failed to obtain a product with the correct melting point since he omits mention of the melting point of his acid chloride.

We prepared pure p-dimethylaminobenzoyl chloride by the method recently described for nicotinic acid chloride [9]. 5 g (0.025 mole) potassium p-dimethylaminobenzoate, dried at 135°, was crushed to a fine powder and placed with 20 ml dry benzene in a small flask with a reflux condenser. Dropwise addition was made to the mixture, with ice cooling and shaking, of a solution of 3.1 g (0.025 mole) oxalyl chloride in 6 ml benzene. Stirring was then continued for another 20 minutes, after which the mixture was heated to the boil and boiled for half an hour. The precipitate of potassium chloride was quickly separated; part of the benzene was distilled off and the acid chloride crystallized. Yield 2.3 g (50%), m.p. 147-148° (147-148° [15]).

Ethoperchlorate of 2-p-dimethylaminophenylbenzoxazole. 1.25 g p-dimethylaminobenzoyl chloride and 0.93 g N-ethyl-o-aminophenol were heated 10 minutes at 180°; during this operation the fused mixture boiled. After cooling, the melt was gently heated with 10 ml anhydrous alcohol and the yellow solution was filtered. The melting point and absorption maximum (300 mμ) of the insoluble residue corresponded to p-dimethylaminophenylbenzoxazole – the product of cleavage of ethyl chloride from the quaternary salt.

Found %: N 11.53, 11.67. $C_{15}H_{14}ON_2$. Calculated %: N 11.77.

Sodium perchlorate solution was added to the yellow filtrate giving a precipitate. The yellow precipitate was twice recrystallized from 80% alcohol. Long orange needles, m.p. 226-227° without decomposition, λ_{max} 400 mμ.

Found %: N 7.58, 7.48. $C_{17}H_{19}O_5N_2Cl$. Calculated %: N 7.64.

2-p-Dimethylaminostyrylbenzothiazole was obtained by the method of Brooker and Sprague [16]; yellow needles, m.p. 206°, λ_{max} 400 mμ (literature data [16]: m.p. 206-208°, λ_{max} in methyl alcohol 400 mμ).

Ethiodide: decomp. p. 237°, λ_{max}530 mμ (λ_{max} in methyl alcohol 524 mμ [16]).

2-p-Dimethylaminostyryl-α-naphthothiazole. 1.5 g 2-methyl-α-naphthothiazole, 1.11 g p-diethylaminobenzaldehyde and 0.22 ml concentrated hydrochloric acid were heated at 100° for 8 hours and at 130° for $3^1/_2$ hours. The product was treated with caustic alkali solution and twice recrystallized from pyridine to give 0.85 g (32%) of yellow crystals with m.p. 220°, λ_{max}370 mμ.

Found %: N 8.28, 8.28. $C_{21}H_{18}N_2S$. Calculated %: N 8.49.

Ethiodide [12]: λ_{max} 537 mμ (λ_{max} in methanol 531 mμ [17]).

2-p-Dimethylaminostyrylbenzoselenazole was obtained by condensation of 2-methylbenzoselenazole with p-dimethylaminobenzaldehyde in presence of concentrated hydrochloric acid. Yellow needles, m.p. 198°, λ_{max} 403 mμ.

Found %: N 8.44, 8.46. $C_{17}H_{16}N_2Se$. Calculated %: N 8.56.

Ethiodide: decomp. p. 237°, λ_{max} in methanol 537 mμ (literature data [17]: 536 mμ).

2-p-Dimethylaminostyrylbenzoxazole was obtained by condensation of 2-methylbenzoxazole with p-dimethylaminobenzaldehyde [18], m.p. 174°, λ_{max} 394 mμ.

Methiodide: m.p. 220°, λ_{max} 495 mμ (λ_{max} in methanol 496 mμ [17]).

The absorption curves were plotted with an SF-4 spectrophotometer in alcohol solutions at concentrations of 10^{-4}M. Solutions of bases in 0.1 N alcoholic solution of sulfuric acid were used for measurement of the absorption curves of the sulfates of the bases. Special measurements of the absorption maxima of one and the same quaternary salt in alcohol and 0.1 N alcoholic sulfuric acid established that the addition to the alcohol of sulfuric acid of that concentration does not alter the maximum of absorption of the salt.

SUMMARY

The absorption maxima of sulfates of 2-p-dimethylaminophenyl derivatives of benzothiazole, 6-methylbenzothiazole, α-naphthothiazole and benzoselenazole in alcoholic solutions are shifted towards the long-wave region in comparison with the absorption maxima of quaternary salts of the same bases. This unusual phenomenon is associated with deviation from coplanarity of the benzene and thiazole (or selenazole) rings in the molecules of the quaternary salts due to steric hindrance.

LITERATURE CITED

[1] D. Crowfoot, Hodgkins and G. Pitt, Ann. Rep. Progr. Chem. 47, 459 (1950).

[2] J. Hofer, R. Grabenstetter and E. Wiig, J. Am. Chem. Soc. 72, 207 (1950).

[3] A. I. Kiprianov, Doctoral Dissertation, Kharkov, (1940) p. 147.

[4] A. I. Kiprianov, L. P. Yakovleva and Yu. S. Rozum, J. Gen. Chem. 22, 305 (1952).

[5] A. I. Kiprianov and I. K. Ushenko, J. Gen. Chem 20, 514 (1950) (T.p. 543).*

[6] L. Brooker, White, R. Sprague, Dent and Van Zandt, Chem. Revs. 41, 347 (1947).

[7] L. Pauling, Nature of the chemical bond (State Chemical Press, 1947) 166-167.

[8] J. Decombe, Bull. Soc. Chim. 1951, 416.

[9] H. Wingbield Jr., W. Harban, and H. Hammer, J. Am. Chem. Soc. 75, 4364 (1953).

[10] M. Bogert and W. Taylor, Coll. Trav. Chim. Tchecoslov. 3, 480 (1931); Chem. Zentr. 1932, I, 679.

[11] R. Hunter, Chem. News 128, 65 (1923); Chem. Zentr. 124, I, 2257.

[12] V. M. Zubarovsky, J. Gen. Chem. 17, 615 (1947).

[13] H. Bauer, Ber. 46, 96 (1913).

[14] F. Stefens and J. Bower, J. Chem Soc. 1949, 2972.

[15] Rivier and Richard, Helv. Chim. Acta 8, 493 (1925).

[16] L. Brooker and R. Sprague, J. Am. Chem. Soc. 63, 3207, 3212 (1941).

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* T. p. = C. B. Translation pagination.

[17] L. Brooker et al. J. Am. Chem. Soc. 73, 5337 (1951).

[18] D. Brown, G. Kon, J. Chem. Soc. 1948, 2153.

Received November 5, 1955

Kiev State University

SYNTHESIS OF 4-METHYL-5-ACETYL-2-AMINOTHIAZOLE AND SOME OF ITS DERIVATIVES

P. M. Kochergin

Although 4-methyl-5-acetylthiazole has been prepared by a number of investigators [1-3], its amino derivative – 4-methyl-5-acetyl-2-aminothiazole (I) – is not described in the literature. We are interested in this compound in connection with the verification of the structure of some 1-acetyl-5-phenyl-(p-nitrophenyl)-2-β-ketoalkylmercaptoimidazoles and of the 2-acyl-3-methyl-5-phenyl-(p-nitrophenyl)-imidazo-(2,1-b)-thiazoles synthesized from them. We also wished to make biological tests of some of its derivatives.

We first attempted to obtain (I) by the simplest method – by heating acetylacetone, thiourea and iodine without a solvent, as in the preparation of other 4-mono- and 4,5-substituted 2-aminothiazoles [4]. In this case we did not succeed in isolating the desired compound from the reaction mass. Substance (I) was obtained in good yield (95-98%) by condensing 3-chloro-2,4-pentanedione with thiourea in aqueous solution. The hydrochloride formed in the reaction is easily separated and purified, after removal of the water, by recrystallation from alcohol, while the base itself is obtained by neutralization of the reaction mass with sodium acetate and recrystallization from 85-90% acetic acid.

4-Methyl-5-acetyl-2-aminothiazole was likewise prepared by bromination of acetylacetone with bromine in chloroform solution followed by treatment of the bromination product with thiourea. The yield is lower by this method because bromination of acetylacetone by bromine goes in more than one direction.

For biological tests we were interested in obtaining the thiosemicarbazone of (I) as well as the sulfamide. Thiosemicarbazones of aromatic aldehydes [5] and aldehydes of the thiazole series [6] are known to possess antitubercular activity and in some cases also antiinfluenzal activity, while 2-(p-aminobenzenesulfamido)-thiazole (nor-sulfazole) and 4-methyl-2-(p-aminobenzenesulfamido)-thiazole (sulfazole) possess high antibacterial activity and are widely used in medical practice. The thiosemicarbazone was prepared by the usual method of reaction of ketone (I) with thiosemicarbazide.

The synthesis of 4-methyl-5-acetyl-2-(p-aminobenzenesulfamido)-thiazole, formerly obtained by condensation of sulfamido derivatives of thiourea with 3-chloro-2,4-pentanedione [7,8], was effected by us by reacting (I) with p-acetylaminobenzenesulfochloride in pyridine and then saponifying the 4-methyl-5-acetyl-2-(p-acetylaminobenzenesulfamido)-thiazole in caustic alkali solution.

The prepared compounds were tested in the department of chemotherapy of our institute for antibacterial activity (range of 18 varieties of microbes)*. The hydrochloride of (I) was found to be generally inactive. The acetyl derivative (4-methyl-5-acetyl-2-acetylaminothiazole) possesses weak activity against the acid-resistant saprophyte B_5, microsporon and achorion. The thiosemicarbazone of (I), apart from activity against the above three microorganisms, is also weakly active against the bacillus of human tuberculosis, the bacillus of avian tuberculosis and trichophyton. 4-Methyl-5-acetyl-2-(p-aminobenzenesulfamide)-thiazole arrests the growth of the enteric bacillus in 1:64,000 dilution, of the bacillus of brushnotyphosus, of Flexner dysenteric bacillus and of proteus vulgaris in 1:16,000 dilution, of staphylococcus aureus, of hemolytic streptococcus and acid-resistant saprophyte B_5 in 1:8,000 dilution, of the bacillus of avian tuberculosis in 1:4,000 dilution and of antrapoid spores and the bacillus of human tuberculosis in 1:2000 dilution.

I am extremely grateful to M. N. Tsukina for providing the opportunity of carrying out this work.

EXPERIMENTAL

4-Methyl-5-acetyl-2-aminothiazole (I). a) To a warm solution of 6 g thiourea in 60 ml water was added 10.7 g 3-chloro-2,4-pentanedione [2], and the mixture carefully (the reaction goes with spontaneous heating) heated to the boil, after which it was boiled for 1 hour (the last 10-15 minutes in presence of active carbon). The solution was then filtered, cooled and neutralized with sodium acetate. The precipitate was filtered, washed with water and dried. Yield 12 g (97.6%) of (I) with m.p. 259-260° (with decomp.); recrystallization from 85-90% acetic acid gave colorless, spindle-shaped crystals with m.p. 260-261° (with decomp.), nearly insoluble in the majority of organic solvents, sparingly soluble in dioxane, pyridine and alcohol, insoluble in water and caustic alkali solution, quite soluble in hydrochloric acid.

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* The investigations were undertaken by S. N. Milovanova and A. A. Mikerina under the direction of G. N. Pershin.

Found %: C 46.10; H 5.40; N 17.70; S 20.59. $C_6H_8ON_2S$. Calculated %: C 46.11; H 5.16; N 17.94; S 20.53.[*]

Hydrochloride: colorless crystals (from alcohol) with m.p. 225-228° (with decomp.).

Found %: Cl 18.40. $C_6H_9ON_2SCl$. Calc. %: Cl 18.41.

Picrate: yellow thread-like crystals (from alcohol) with m.p. 199-200° (with decomp.).

Found %: N 17.64. $C_{12}H_{11}O_8N_5S$. Calculated %: N 18.18.

b) A solution of 86.4 g bromine in 50 ml chloroform was added in the course of 1 hour to a solution of 54 g acetylacetone in 220 ml anhydrous chloroform with cooling to -10° and energetic stirring. At the end of the reaction the hydrogen bromide and the solvent were distilled off in vacuum, and the brown, liquid residue gradually add to 41 g thiourea in 180 ml water, after which the mixture was heated as in the preceding experiment. The brown solution was then filtered from the carbon, evaporated in vacuum to small volume and cooled; the precipitate was filtered, washed with acetone and dried. Another few grams of this substance was obtained by evaporating the mother liquor to a small volume. Two recrystallizations from alcohol gave the hydrobromide of (I) in the form of rectangular plates with m.p. 247-249° (with decomp.).

Found %: Br 33.73. $C_6H_9ON_2SBr$. Calculated %: Br 33.71.

The base was obtained by addition of sodium acetate to an aqueous solution of the hydrobromide; m.p. 260-261° (with decomp.). A mixture with (I) obtained by method (a) melted at 260-261° (with decomp.).

4-Methyl-5-acetyl-2-acetylaminothiazole. 9 ml acetic anhydride was added to 1.7 g of (I) and the mixture was heated. When the violent reaction had ended, the solution was cooled, and the precipitate was filtered, washed with ether and dried. Yield 1.8 g (85.6%) of substance with m.p. 227-228°; recrystallization from alcohol gave colorless prisms with m.p. 228-229°; soluble in alcohol, dioxane, glacial acetic acid and hydrochloric acid, sparingly soluble in acetone and chloroform, insoluble in carbon tetrachloride, benzene, dichloroethane, ethyl acetate, water and caustic alkali solution.

Found %: N 14.35. $C_8H_{10}O_2N_2S$. Calculated %: N 14.14.

4-Methyl-5-acetyl-2-aminothiazole thiosemicarbazone. A mixture of 4.1 g of (I) and 2.4 g thiosemicarbazide in 50 ml glacial acetic acid was boiled for 30 minutes (the last 10 minutes in presence of active carbon). The solution was then filtered and cooled; the precipitate was filtered, washed with ether and dried. Another few grams of this substance was obtained by evaporating the mother liquor to a small volume and washing the residue with ether. Yield 6 g (97%), m.p. 194-197° (with decomp.); recrystallization from alcohol gave pale-yellow prisms with m.p. 203-204° (with decomp.); the compound is nearly insoluble in the majority of organic solvents, water and caustic alkali solution, sparingly soluble in alcohol, easily soluble in glacial acetic acid and hydrochloric acid.

Found %: S 28.01. $C_7H_{11}N_5S_2$. Calculated: S 27.97.

4-Methyl-5-acetyl-2-(p-aminobenzenesulfamido)-thiazole. 8.5 g p-acetylaminobenzenesulfochloride was added in the course of 10 minutes with stirring to a suspension of 4.1 g of (I) in 45 ml pyridine, after which the mixture was heated at 60-62° and stirred for $1\frac{1}{2}$ hours. 125 ml water was then added and the mixture was cooled and neutralized with hydrochloric acid until acid to Congo; the precipitate (3.1 g) of 4-methyl-5-acetyl-2-(p-acetylaminobenzenesulfamido)-thiazole was filtered, washed with alcohol, then with ether and dried. Pale-yellow crystals, soluble in caustic alkali solution, nearly insoluble in alcohol and dilute hydrochloric acid.

3 g 4-methyl-5-acetyl-2-(p-acetylaminobenzenesulfamido)-thiazole in 30 ml 4% aqueous sodium hydroxide solution was boiled for 2 hours (the last 30 minutes in presence of active carbon). The solution was then

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[*] All analyses were carried out in the microanalytical laboratory of our institute.

cooled, filtered from carbon and neutralized with hydrochloric acid until acid to Congo; the excess of acid was then neutralized with sodium acetate. The precipitate was filtered off, washed with water and recrystallized from alcohol. Pale-yellow prisms with m.p. 213-214° (with decomp.), readily soluble in caustic alkali solution, sparingly soluble in alcohol, acetone, dioxane and glacial acetic acid, insoluble in dilute hydrochloric acid, chloroform, ether, benzene, dichloroethane, carbon tetrachloride, ethyl acetate and water.

Found %: C 46.37; H 4.35; N 13.19; S 20.34. $C_{12}H_{13}O_3N_3S_2$. Calculated %: C 46.26; H 4.21; N 13.50; S 20.60.

SUMMARY

4-Methyl-5-acetyl-2-aminothiazole and some of its derivatives substituted at the amino and carbonyl groups were prepared.

LITERATURE CITED

[1] P. Baumgarten, A. Dornow, K. Gutschmidt, and H. Krehl, Ber. 75B, 442 (1942).

[2] E. R. Buchman, and E. M. Richardson, J. Am. Chem. Soc. 67, 398 (1945).

[3] K. Ganapathi, and A. Venkataraman, Proc. Indian Acad. Sci. 22A, 343, 362 (1945); Chem. Abs. 40, 4056, 4959 (1946).

[4] R. M. Dodson, and L. C. King, J. Am. Chem. Soc. 67, 2242 (1945).

[5] Thiosemicarbazones, Symposium on Chemistry and Medicine, (Moscow, 1954).

[6] H. Taniyama, B. Yasui, F. Inoue, J. Pharm. Soc. Japan, (1953) 73, 276; Chem. Abs. 48, 2045 (1954).

[7] Hungarian Pat. 133971 (1948); Ch. A., 43, 3852 (1949).

[8] British Pat. 620654 (1949); Chem. Abs. 44, 659 (1950).

Received October 28, 1955

All-Union S. Ordzhonikidze Institute of
Pharmaceutical Chemical Research

SYNTHESIS OF β-(N-2-CHLOROPHENOTHIAZYL)-PROPIONIC ACID AND ITS DERIVATIVES AND DERIVATIVES OF β-N-PHENOTHIAZYL-PROPIONIC ACID

N. V. Savitskaya, Yu. S. Tsizin and M. N. Shchukina

The objective of this work was the synthesis of β-(N-2-chlorophenothiazyl)-propionic acid and its derivatives for pharmacological and antibacterial investigations. The starting substance for our investigations was 2-chlorophenothiazine which is used for the synthesis of N-(3'-dimethylaminopropyl)-2-chlorophenothiazine, a well-known medicinal preparation (aminasine, largaktyl, megaphene, chloropromasin). The literature does not contain a detailed description of the synthesis of 2-chlorophenothiazine [1]. It was prepared by condensation of 3-chlorodiphenylamine with sulfur and separation of the resultant 2- and 4-chlorophenothiazines by recrystallization from 50% aqueous acetone or chlorobenzene. Cyanoethylation of 2-chlorophenothiazine under the conditions described for phenothiazine [2] gave β-(N-2-chlorophenothiazyl)-propionitrile. Whereas the saponification of β-(N-phenothiazyl)-propionitrile goes with 65% yield, the saponification of β-(N-2-chlorophenothiazyl)-propionitrile under the same conditions [2] only leads to an insignificant yield of the corresponding acid; moreover, cleavage of the molecule takes place with formation of 2-chlorophenothiazine. Attempts to saponify the nitrile with sulfuric acid of various strengths resulted in the original substance being recovered unchanged.

The acid was obtained in good yield by saponification of its ethyl ester, which was synthesized by heating a mixture of nitrile and alcohol in a sealed ampoule in presence of conc. H_2SO_4. Reduction of the nitrile in an autoclave at 100 atm. in presence of Ni gave N-(3'-aminopropyl)-2-chlorophenothiazine. The amide and hydrazide of β-(2-chlorophenothiazyl)-propionic acid were obtained by the usual methods. Reaction of a benzene solution of β-(n-2-chlorophenothiazyl)-propionic acid with PCl_5 gave the acid chloride which was subjected, without isolation, to condensation with ethylene chlorohydrin [3]. Condensation of the resultant β'-chloroethyl ester of β-(N-2-chlorophenothiazyl)-propionic acid with unsymmetrical dimethylhydrazine gave the corresponding hydrazinium salt, formed in satisfactory yield only by heating in a sealed ampoule.

It was also of interest to prepare some derivatives of β-(N-phenothiazyl)-propionic acid which have not been described in the literature. The preparation of esters of this acid, formerly realized by reaction of the silver salt of the acid with alkyl iodides [4], was effected by heating an alcoholic solution of the acid in presence of conc. H_2SO_4, a yield of 83-84% being obtained. The acid amide was prepared by reacting the acid chloride with ammonia. The hydrochloride of the dimethylaminoethyl ester of β-(N-phenothiazyl)-propionic acid and the hydrazide of this acid were synthesized by the usual method. The β'-chloroethyl ester of β-(N-phenothiazyl)-propionic acid was prepared under the same conditions as for the corresponding derivative of β-(N-2-chlorophenothiazyl)-propionic acid. Condensation of the β'-chloroethyl ester of β-(N-phenothiazyl)-propionic acid with unsymmetrical dimethylhydrazine was carried out under the conditions described for the corresponding derivatives of benzhydrol [3].

EXPERIMENTAL

2-Chlorophenothiazine. A mixture of 17.4 g 3-chlorodiphenylamine, 5.8 g powdered sulfur and 0.2 g iodine was heated at 160-180° for $1^1/_4$ hours until hydrogen sulfide ceased to come off. The reaction mass was then recrystallized from chlorobenzene (60 ml) or from 50% aqueous acetone. Yield 12.1 g (60.5%), m.p. 191-194°. Recrystallization from toluene gave a yellow-green crystalline powder with m.p. 199-200.5° (the literature reports 196-197°). Soluble in the majority of organic solvents, sparingly soluble in ligroin and water.

β-(N-2-chlorophenothiazyl)-propionitrile. To a mixture of 10 g 2-chlorophenothiazine, 30 ml acrylonitrile and 0.1 g hydroquinone at room temperature and with stirring was added 2 ml anhydrous alcoholic solution of Rodionov catalyst in the course of 2 minutes. The catalyst was prepared from 0.76 g of trimethylphenylammonium p-toluenesulfonate. After addition of the catalyst, the reaction mass thickened, and its temperature rose to 65°. The reaction mass was thereupon heated at 80° for $1^1/_2$ hours; after cooling, the precipitate was filtered off and washed with ether. Yield 10 g (81%) of substance with m.p. 182-185°. Recrystallization from glacial acetic acid gave white needles with m.p. 188-189° (7.5 g, 61%), soluble in dichloroethane, acetone, chloroform, ethyl acetate, poorly soluble in alcohol and carbon tetrachloride, insoluble in water and ether.

Found %: N 10.08; Cl 12.34. $C_{15}H_{11}N_2ClS$. Calculated %: N 9.76; Cl 12.32.

β-(N-2-Chlorophenothiazyl)-propionic acid. A mixture of 25.5 g β-(N-2-chlorophenothiazyl)-propionitrile, 8 ml conc. sulfuric acid and 50 ml ethyl alcohol was heated for 6 hours in a sealed ampoule at a bath temperature of 130-140°. The reaction mass was then rendered alkaline with 100 ml of 25% aqueous potassium hydroxide and boiled for 6 hours, after which the reaction mass was diluted with 300 ml water and acidified with hydrochloric acid. The resultant precipitate was separated. Yield 23.7 g (87%), m.p. 150-152°. Two recrystallizations from methanol gave colorless scales with m.p. 156.5-158°, soluble in the common organic solvents, insoluble in water.

Found %: Cl 11.89; N 4.70. Equiv. 304.5. $C_{15}H_{12}NO_2SCl$. Calculated %: Cl 11.59; N 4.58. Equiv. 305.78.

Ethyl ester of β-(N-2-chlorophenothiazyl)-propionic acid. A mixture of 16 g β-(N-2-chlorophenothiazyl)-propionitrile, 34 ml ethyl alcohol and 4.5 ml conc. sulfuric acid was heated in an ampoule for 6 hours at 130-140°. The reaction mass was then poured into a large volume of water and extracted with ether. The ether layer was washed with bicarbonate and then with water and dried over sodium sulfate. The ether was driven off and the residue distilled in vacuum (0.4 mm). Yield 16 g (86%) with b.p. 205-209°. After two recrystallizations from ligroin, colorless needles were obtained with m.p. 64.5-66°, readily soluble in the usual organic solvents, insoluble in water.

Found %: N 4.23; Cl 10.94. $C_{17}H_{16}O_2NSCl$. Calculated %: N 4.19; Cl 10.62.

N-(3'-aminopropyl)-2-chlorophenothiazine. A solution of 10 g β-(N-2-chlorophenothiazyl)-propionitrile in 200 ml alcohol was reduced in presence of skeletal nickel catalyst (2 g) and gaseous ammonia (10 atm.) at 100-110° and 90 atm. pressure. Hydrogen was absorbed for 3 hours and the calculated amount was absorbed. The solvent was then driven off. The residue (approx. 10 g) was a transparent, faint-green, syrupy liquid. It was dissolved in anhydrous alcohol, and an anhydrous alcoholic solution of hydrogen chloride was added until the reaction was acid to Congo. Yield 8.9 hydrochloride with m.p. 216-228°. Several recrystallizations from anhydrous alcohol gave slightly colored needles with m.p. 233-235°, poorly soluble in water and hydrochloric acid.

Found %: N 8.54; Cl 21.56. $C_{15}H_{15}N_2SCl \cdot HCl$. Calculated %: N 8.57; Cl 21.62.

β-(N-2-Chlorophenothiazyl)-propionamide. A solution of 2 g ethyl ester of β-(N-2-chlorophenothiazyl)-propionic acid in 15 ml of anhydrous alcohol saturated with ammonia was heated in an ampoule for 24 hours on a boiling water bath. The alcohol was then driven off and the residue (a glassy mass) was made to crystallize by trituration with ether. Yield 0.6 g (33%), m.p. 142-145°. Two recrystallizations from benzene gave a colorless powder with m.p. 143.5-145.5°, soluble in alcohol, chloroform and dichloroethane, insoluble in ether and water.

Found %: N 9.44; Cl 11.50. $C_{15}H_{13}ON_2ClS$. Calculated %: N 9.19; Cl 11.63.

Hydrazide of β-(N-2-chlorophenothiazyl)-propionic acid. A mixture of 5 g ethyl ester of β-(N-2-chlorophenothiazyl)-propionic acid, 30 ml alcohol and 3 ml 65% hydrazine hydrate was heated for 28 hours on a boiling water bath. The alcohol was driven off and the oily residue thoroughly washed with water. The residue (approx. 4 g) solidified and had m.p. 120-123°. It was twice recrystallized from methanol to give a colorless crystalline powder with m.p. 132.5-133.5°, readily soluble in alcohol, benzene, dichloroethane and glacial acetic acid, insoluble in water and ether.

Found %: N 13.44; Cl 11.24. $C_{15}H_{14}ON_3ClS$. Calculated %: N 13.14; Cl 11.12.

p-Acetaminobenzalhydrazide of β-(N-2-chlorophenothiazyl)-propionic acid: colorless crystalline powder with m.p. 236-237° (from glacial acetic acid).

Found %: N 11.83; Cl 7.38. $C_{24}H_{21}N_4O_2SCl$. Calculated %: N 12.03; Cl 7.64.

β'-Chloroethyl ester of β-(N-2-chlorophenothiazyl)-propionic acid. A suspension of 19 g β-(N-2-chlorophenothiazyl)-propionic acid and 13.2 g PCl_5 in 360 ml dry benzene was vigorously shaken at room temperature for 10 minutes. The whole of the acid went into solution, which acquired a dark-red color. After filtration of the solution, the benzene was removed in vacuum at 30-40°, and the residue was thoroughly freed from $POCl_3$ by three additions of benzene followed by distillation. Addition was then made to the crystalline residue of 55 ml dry benzene and 5.5 g ethylene chlorohydrin, and the mixture refluxed for 11 hours. The benzene was then taken off in vacuum, and the residue crystallized when rubbed. It was recrystallized from ethyl acetate. Yield 16 g (70%), m.p. 82-84°. Recrystallization from ethyl acetate gave a colorless crystalline powder with m.p. 82-84°, soluble in alcohol, ether, benzene and ligroin , insoluble in water.

Found %: N 3.94; Cl 19.44. $C_{17}H_{15}Cl_2O_2NS$. Calculated %: N 3.8; Cl 19.23.

1,1-Dimethyl-1-{2'[β-(N-2''-chlorophenothiazyl)-propionyl]-hydroxyethyl} - hydrazonium chloride. A mixture of 5 g β'-chloroethyl ester of β-(N-2-chlorophenothiazyl)- propionic acid and 1.4 ml unsymmetrical dimethylhydrazine was heated in an ampoule on a boiling water bath for 5½ hours. The reaction mass was then dissolved in 10 ml anhydrous alcohol, and to the solution was added 200 ml dry ether. An oily substance separated out and crystallized on standing in a refrigerator. It was recrystallized from a mixture of 40 ml anhydrous alcohol and 25 ml ethyl acetate. Yield 2.7 g (46%), m.p. 181.5-183.5°. A second recrystallization from alcohol-ethyl acetate gave a colorless substance with m.p. 184-185°, soluble in alcohol and water, insoluble in ether, acetone and chloroform.

Found %: N 9.42; Cl 16.50. $C_{19}H_{23}O_2Cl_2N_3S$. Calculated %: N 9.81; Cl 16.56.

Methyl β-(N-phenothiazyl)-propionate. A mixture of 16 g β-(N-phenothiazyl)-propionic acid, 40 ml methanol and 4 ml conc. sulfuric acid was heated at the boil for 6 hours. The reaction mass was then poured into a large volume of water and extracted with ether; the ether layer was washed with bicarbonate and then with water, the ether was distilled off and the residue distilled. Yield 14 g (83%), b.p. 210-214° (1 mm). Recrystallization from alcohol gave colorless crystals with m.p. 64.5-65.5° (the literature reports 64-65°), soluble in the usual organic solvents, insoluble in water.

Ethyl β-(N-phenothiazyl)-propionate. This was prepared under the conditions described above for the ethyl ester of β-(N-2-chlorophenothiazyl)-propionic acid from 4 g β-(N-phenothiazyl)-propionitrile, 1.3 ml conc. sulfuric acid and 9 ml alcohol. Yield 4 g (84%), b.p. 195-202° (0.5 mm). Recrystallization from ethyl alcohol gave white needles with m.p. 63.5° (the literature reports 64°).

β-(N-Phenothiazyl)-propionamide. A benzene solution of the acid chloride was obtained from 2 g β-(N-phenothiazyl)-propionic acid, 1.6 g PCl_5 and 40 ml benzene, as described above. Gaseous ammonia was then passed into the solution until completely decolorized; it was then diluted with water and the benzene layer was separated. After removal of the benzene, the residue was recrystallized 3 times from aqueous alcohol. Yield 0.5 g (25%), m.p. 125-126°. A white crystalline substance, readily soluble in alcohol, benzene and ligroin, insoluble in water.

Found %: C 66.24; H 4.95; N 9.97. $C_{15}H_{14}ON_2S$. Calculated %: C 66.65; H 5.22; N 10.35.

Hydrazide of β-(N-phenothiazyl)-propionic acid. A mixture of 7.75 g ethyl β-(N-phenothiazyl)-propionate and 4 ml 65% hydrazine hydrate was heated at the boil for 28 hours. The alcohol was then removed in vacuum and several additions of water followed by distillation of the water were made to the oily residue. The residue solidified on cooling and was dried and twice recrystallized from benzene. Yield 5.1 g (69%), m.p. 98-99° (with decomp.). The compound is readily soluble in alcohol, benzene and chloroform, insoluble in ether and water.

Found %: N 14.55. $C_{15}H_{15}ON_3S$. Calculated %: N 14.70.

p-Acetaminobenzalhydrazide of β-(N-phenothiazyl)-propionic acid: a nearly colorless crystaline substance, m.p. 192-193° (from glacial acetic acid).

Found %: N 13.26. $C_{24}H_{22}O_2N_4S$. Calculated %: N 13.01.

4-Hydroxy-3-methoxybenzalhydrazide of β-(N-phenothiazyl)-propionic acid: colorless needles with m.p. 200.5-202° (from glacial acetic acid).

Found %: N 9.84. $C_{23}H_{21}O_3N_3S$. Calculated %: N 10.00.

Hydrochloride of the dimethylaminoethyl ester of β-(N-phenothiazyl)-propionic acid. A benzene solution of the acid chloride of this acid was obtained, in the manner described above, from 10 g β-(N-phenothiazyl)-propionic acid by reaction with 8 g PCl_5 in 250 ml dry benzene. 15 g dimethylaminoethanol was then added to the solution, and the mixture was left overnight. The reaction mass was then diluted with 200 ml water and the benzene layer was separated, washed with bicarbonate and with water and dried over magnesium sulfate. After removal of the benzene, the oily residue was distilled to give 9.3 g (66%), b.p. 214-216°. To the benzene solution (20 ml) of the ester base (9.3 g) was added an alcoholic solution of hydrogen chloride until acid to Congo and 15 ml anhydrous ether until crystallization commenced. Yield 9.1 g, m.p. 140.5-142°. Recrystallization from chlorobenzene gave white crystals with m.p. 141.5-142.5°, soluble in alcohol, chlorobenzene and water, insoluble in ether and benzene.

Found %: N 7.55; Cl 9.26. $C_{19}H_{22}O_2N_2S \cdot HCl$. Calculated %: N 7.40; Cl 9.36.

β'-Chloroethyl ester of β-(N-phenothiazyl)-propionic acid. A benzene solution of the acid chloride of this acid was prepared, in the manner described above, from 30 g β-(N-phenothiazyl)-propionic acid in 400 ml dry benzene and 24 g PCl_5. After filtration of the solution, the benzene was taken off in vacuum on a bath at 30-40°, and dry benzene was added 3 times (100 ml each time) to the residue and then distilled off. Afterwards, addition was made to the residue of 60 ml benzene and 9.6 ethylene chlorohydrin, and the mixture boiled 10 hours. The benzene and excess ethylene chlorohydrin were then removed in vacuum, and the residue (an oil) was crystallized by rubbing with ligroin. Yield 26.2 g (70%), m.p. 72-74.5° Two recrystallizations from ethyl alcohol gave colorless crystals with m.p. 75-76°.

Found %: N 4.05; Cl 10.75. $C_{17}H_{16}O_2NSCl$. Calculated %: N 4.19; Cl 10.62.

1,1-Dimethyl-1-{2'[β-(N-phenothiazyl)-propionyl] -hydroxyethyl} -hydrazonium chloride. A mixture of 17 g β'-chlorethyl ester of β-(N-phenothiazyl)-propionic acid and 5 ml unsymmetrical dimethylhydrazine was kept for 3 days at room temperature followed by 3 days in a refrigerator. The reaction mass was then dissolved in 20 ml anhydrous alcohol and 15 ml ether was added until crystallization commenced. Yield 5 g, m.p. 169.5-171.5° (with decomp.). Starting substance was recovered on evaporating the filtrate. Recrystallization from anhydrous alcohol gave a colorless, crystalline powder with m.p. 174.5-175.5°, soluble in alcohol and water, insoluble in ether, benzene and ethyl acetate.

Found %: N 10.40; Cl 8.87. $C_{19}H_{24}O_2N_3SCl$. Calculated %: N 10.66; Cl 9.00.

SUMMARY

The following were synthesized: 1) β-(N-2-chlorophenothiazyl)-propionic acid, its ethyl ester, amide, hydrazide and the corresponding hydrazone, and nitrile (reduction of the latter gave N-(3'-aminopropyl)-2-chlorophenothiazine), the β'-chloroethyl ester of β-(N-2-chlorophenothiazyl)-propionic acid, and the product of its condensation with unsymmetrical dimethylhydrazine; 2) the dimethylaminoethyl ester of β-(N-phenothiazyl)-propionic acid, its amide and hydrazide, and the corresponding hydrazones, the β'-chloroethyl ester of β-(N-phenothiazyl)-propionic acid and the product of its condensation with unsymmetrical dimethylhydrazine.

LITERATURE CITED

[1] P. Charpentier, P. Gailliot, R. Jacob et al. Compt. rend. 235, 59 (1952).

[2] N. L. Smith, J. Org. Chem. 15, 1125 (1950).

[3] See : M. Protiva and O. Exner, Chem. listy 47, 1481 (1953).

[4] A. Mackie and A. A. Gutler, J. Chem. Soc. 1954, 2577.

Received October 25, 1955

All-Union S. Ordzhonikidze Institute of
Pharmaceutical Chemical Research

INVESTIGATIONS IN THE IMIDAZOLE SERIES

VI. THE ACTION OF BROMOACETALDEHYDE AND ITS DERIVATIVES ON SOME 2-MERCAPTOIMIDAZOLES

P. M. Kochergin and M. N. Shchukina

The action of bromoacetaldehyde or of other α-haloaldehydes on 2-mercaptoimidazoles has not been described in the literature. The reaction is of definite interest, since the action of bromoacetaldehyde on 2-mercaptoimidazoles can be expected to lead to imidazo-(2,1-b)-thiazoles without substituents in the thiazole ring. Apart from this, it would be of interest to establish whether in the present case the intermediate imidazolyl-2-mercaptacetaldehydes could be isolated. These are analogous in structure to the products of reaction of 2-mercaptoimidazoles with α-haloketones – 2-β-ketoalkyl(aryl)-mercaptoimidazoles [1-3]. Due to the greater reactivity of the aldehyde group in comparison with the ketone, the possibility of instantaneous cleavage of a molecule of water with formation of imidazo-(2,1-b)-thiazoles had to be taken into consideration.

In the present work we studied the action of bromoacetaldehyde on 4(5)-phenyl- and 4(5)-p-nitrophenyl-2-mercaptoimidazoles [4]. In the case of 4(5)-phenyl-2-mercaptoimidazole we also studied the action of the dimethylacetal and diethlacetal of bromoacetaldehyde and of α,β-dibromoethyl ether.

Reaction of 4(5)-phenyl- and 4(5)-p-nitrophenyl-2-mercaptoimidazoles with bromoacetaldehyde, which was prepared without isolation in the free state by heating α,β-dibromodiethyl ether in water, gave crystalline compounds whose elementary analysis corresponded to the respective imidazolyl-2-mercaptoacetaldehydes. The product of reaction of 4(5)-phenyl-2-mercaptoimidazole with bromoacetaldehyde was studied the most thoroughly. This pure crystalline compound does not give sufficiently typical reactions for the aldehyde group. It reacts with thiosemicarbazide, phenylhydrazine and 2,4-dinitrophenylhydrazine, but crystalline derivatives of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde could not be isolated. It does not give a silver mirror with ammoniacal silver oxide but deposits a brown, flocculent precipitate. With fuchsinesulfurous acid the crimson-violet color does not appear at once but only after some time and gradually. The infrared spectrum of this compound (Fig. 1), plotted in the solid state, does not contain the absorption band of the carbonyl group (at 1740-1760 cm^{-1}). The curve is generally very similar to that of 3-methoxy-6-phenylimidazo-(2,1-b)-thiazoline (Fig. 2), whose synthesis will be described below, and differs markedly from the spectrum of 4(5)-pheny-2-acetonyl-mercaptoimidazole [3] (Fig. 3) as a compound containing the carbonyl group.* On the basis of the physicochemical properties of this compound we may suggest that in the solid state it has the structure of 3-hydroxy-6-phenylimidazo-(2,1-b)-thiazoline. In solution, this compound probably isomerizes partially to 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde. 3-Hydroxy-6-p-nitrophenylimidazo-(2,1-b)-thiazoline possesses similar properties.

It was earlier established that 2-β-ketoalkylmercaptoimidazoles easily lose a molecule of water when boiled with hydrochloric acid [3] or when heated to 95-100° with 85% phosphoric acid [5], and are transformed into imidazo-(2,1-b)-thiazoles. 3-Hydroxy-6-phenyl(p-nitrophenyl)-imidazo-(2,1-b)-thiazolines do not split off water when heated with the above-mentioned acids and are recovered unchanged. Only under the action of phosphorus oxychloride or concentrated sulfuric acid do they split off a molecule of water with facility and undergo transformation respectively into 6-phenyl- and 6-p-nitrophenylimidazo-(2,1-b)-thiazoles. Treatment of 3-hydroxy-6-phenylimidazo-(2,1-b)-thiazoline with concentrated sulfuric acid leads, as in the case of 4(5)-phenyl-2-β-ketoalkylmercaptoimidazoles [6], not only to cleavage of a molecule of water but also to subsequent sulfonation of the 6-phenylimidazo-(2,1-b)-thiazole to form 6-p-sulfophenylimidazo-(2,1-b)-thiazole.

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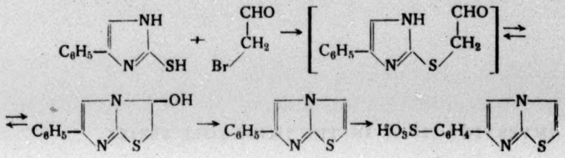
* All the spectra were plotted in the physical chemistry laboratory of our institute by Yu. N. Sheinker.

$$CH_2BrCHBrOC_2H_5 + H_2O \rightarrow CH_2BrCHO + C_2H_5OH + HBr$$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SH
CHO
CH2
Br
NH
CHO
C6H5
N
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CH2
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OH
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S
N
HO3S—C6H4
N
S

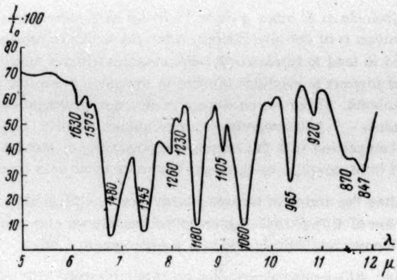


Fig. 1. Infrared spectrum of 3-hydroxy-6-phenylimidazo-(2,1-b)-thiazoline (in vaseline oil).

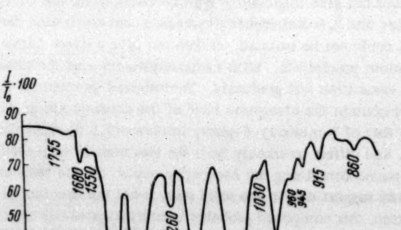


Fig. 2. Infrared spectrum of 3-methoxy-6-phenylimidazo-(2,1-b)-thiazoline (in vaseline oil).

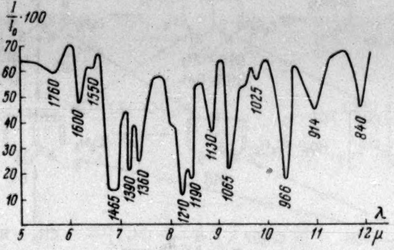


Fig. 3. Infrared spectrum of 4(5)-pheny-2-acetonyl-mercaptoimidazole (in vaseline oil).

As will be shown in the next communication, 4(5)-phenyl(p-nitrophenyl)-2-β-ketoalkyl(aryl)-mercaptoimidazoles react with acetic anhydride to give crystalline N-acetyl derivatives substituted at the imino group of the imidazole ring. 3-Hydroxy-6-phenyl(p-nitrophenyl)-imidazo-(2,1-b)-thiazolines are recovered unchanged after treatment with acetic anhyride, which behavior is likewise evidence of their bicyclic structure.

Since 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde was found not to exist in the individual state and readily isomerized to 3-hydroxy-6-phenylimidazo-(2,1-b)-thiazoline, it was of interest to prepare acetals of this aldehyde and to study their properties and transformation. Reaction of 4(5)-phenyl-2-mercaptoimidazole with the dimethyl- and diethylacetal of bromoacetaldehyde in the corresponding alcohols in presence of the equivalent amount of the corresponding sodium alkoxides gave the dimethyl- and diethyl- acetals of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde. These compounds are colorless oils which decompose when an attempt is made to distill them in vacuum. The second one was characterized as the picrate.

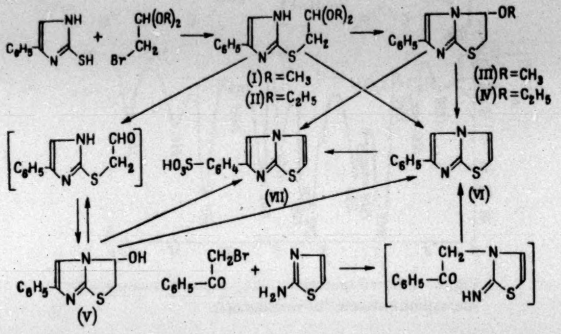
Treatment of the dialkylacetals of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde with dilute hydrochloric acid or alcoholic hydrogen chloride in the cold does not lead to formation of the hydrochlorides of the respective acetals but to hydrolysis with formation of one and the same hydrochloride of 3-hydroxy-6-phenylimidazo-(2,1-b)-thiazoline. The same compound is also formed on boiling the dialkylacetals of 4 (5)-phenylimidazolyl-2-mercaptoacetaldehyde with concentrated hydrochloric acid.

Treatment of the dialkylacetals of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde at 30-50° with concentrated sulfuric acid gives 6-phenylimidazo-(2,1-b)-thiazole, but the yield is very low due to resinification.

Since phosphorus oxychloride was found to be the most convenient agent for cleavage of a molecule of water from 2-β-ketoalkyl-(aryl)-mercaptoimidazoles [1, 2, 5] and from 3-hydroxy-(2,1-b)-thiazolines, it was of interest to study its action on the acetal of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde. Boiling of the dimethyl- and diethylacetals of 4(5)-phenyl-2-mercaptoacetaldehyde with phosphorus oxychloride for $1^1/_2$ hours gave not 6-phenylimidazo-(2,1-b)-thiazole, as was to be expected, but products of removal from the original acetals of only one molecule of alcohol – 3-methoxy- and 3-ethoxy-6-phenylimidazo-(2,1-b)-thiazolines. Another possible structure of these compounds as S-substituted vinyl ethers is ruled out because they do not contain a double bond in the side chain or an imino group in the imidazole ring. The bicyclic structure of 3-alkoxy-6-phenylimidazo-(2,1-b)-thiazolines is likewise consistent with physico-chemical data. The infrared spectrum of 3-methoxy-6-phenylimidazo-(2,1-b)-thiazoline is markedly different from the spectrum of 4(5)-phenyl-2-ethylmercaptoimidazole [4] (Fig. 4) as a compound with an open side chain and, as indicated above, is similar to the spectrum of 3-hydroxy-6-phenylimidazo-(2,1-b)-thiazoline.

Treatment of 3-alkoxy-6-phenylimidazo-(2,1-b)-thiazolines with concentrated sulfuric acid at 30-35° readily leads to cleavage of a molecule of alcohol with formation of 6-phenylimidazo-(2,1-b)-thiazole. At

95-100°, apart from loss of an alcohol molecule, sulfonation of the 6-phenylimidazo-(2,1-b)-thiazole occurs with formation of 6-p-sulfophenylimidazo-(2,1-b)-thiazole. The latter compound was also obtained directly by sulfonation of 6-phenylimidazo-(2,1-b)-thiazole.



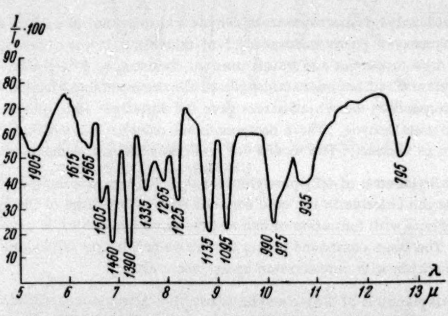
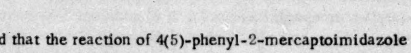
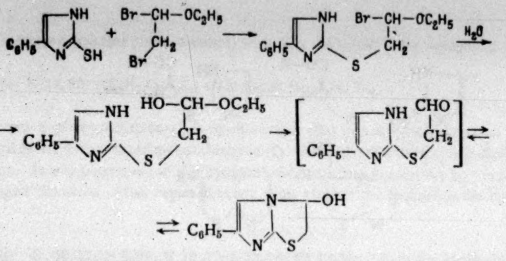


Fig. 4. Infrared spectrum of 4(5)-phenyl-2-ethylmercaptoimidazole (in vaseline oil).

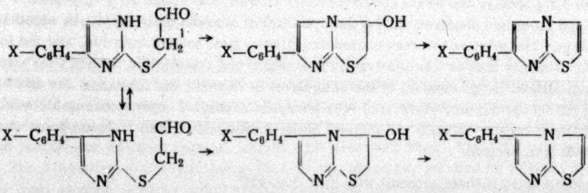
It may be assumed that the reaction of 4(5)-phenyl-2-mercaptoimidazole with α,β-dibromodiethyl ether in anhydrous benzene gives 2-ethoxy-6-phenylimidazo-(2,1-b)-thiazoline, isomeric with 3-ethoxy-6-phenylimidazo-(2,1-b)-thiazoline.



In this case, however, also when carrying out the reaction in water, we isolated 3-hydroxy-6-phenylimidazo-(2,1-b)-thiazoline. The reaction probably goes according to the following scheme:



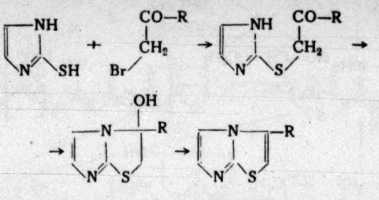
In the isomerization of 4(5)-phenyl(p-nitrophenyl)-2-mercaptoacetaldehyde to 3-hydroxyimidazo-(2,1-b)-thiazoline, just as in the cleavage of the molecule of alcohol from dialkylacetals of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde, the formation of two isomeric imidazo-(2,1-b)-thiazolines is theoretically possible, cleavage from which of a molecule of water or a second molecule of alcohol should lead likewise to two isomeric imidazo-(2,1-b)-thiazoles: 5-phenyl(p-nitrophenyl)- and 6-pheny(p-nitrophenyl)-imidazo-(2,1-b)-thiazoles.



In none of our experiments, however, did we succeed in isolating two isomers.

The structure of the prepared 6-phenyl- and 6-p-nitrophenylimidazo-(2,1-b)-thiazoles was proved by reverse synthesis of these compounds from 2-aminothiazole and α-bromoacetophenone and its p-nitro derivative. The compounds prepared by this route were identical with the substances synthesized from 4(5)-phenyl- and 4(5)-p-nitrophenyl-2-mercaptoimidazoles. The position of the phenyl and p-nitrophenyl radicals in 3-hydroxy- and 3-alkoxyimidazo-(2,1-b)-thiazolines is not in doubt because of the transformation of these compounds into 6-phenyl- and 6-p-nitrophenylimidazo-(2,1-b)-thiazoles. We did not verify the structure of 6-p-sulfophenylimidazo-(2,1-b)-thiazole; by analogy, however, with the sulfonation of 3-methyl-6-phenylimidazo-(2,1-b)-thiazole [6], we may assume that also in the present case the sulfo group is in the para-position of the benzene ring.

The study of the action of α-halocarbonyl compounds on 2-mercaptoimidazoles enables us to draw some conclusions about the mechanism of closure of the thiazole ring during the preparation of imidazo-(2,1-b)-thiazoles. As was shown earlier, the first stage of the interaction of 2-mercaptoimidazoles with α-haloketones is the formation of S-β-carbonyl compounds [1-3]. The action of bromoacetaldehyde on 2-mercaptoimidazoles provides evidence that the next stage of closure of the thiazole ring is migration of the hydrogen of the imino group of the imidazole ring to the oxygen atom of the carbonyl group, and is followed by closure of the hydroxythiazoline ring. The 3-hydroxyimidazo-(2,1-b)-thiazolines lose a molecule of water and are transformed into imidazo-(2,1-b)-thiazoles. Consequently the mechanism of closure of the thiazole ring may be represented by the following scheme:



It is highly probable that a similar mechanism is applicable to the formation of thiazole derivatives in condensation of thiourea or thioamides of carboxylic acids with α-halocarbonyl compounds.

Some of the compounds that we prepared (V, VII, IX and the hydrochloride of III) (see below) were tested for antibacterial activity in the department of chemotherapy of the All-Union Institute of Pharmaceutical Chemical Research (range of 16 varieties of organisms). These compounds are lacking in high antimicrobial activity.*

EXPERIMENTAL

Diethylacetal of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde (II). To a solution of sodium ethoxide, prepared from 1.3 g sodium and 85 ml anhydrous ethyl alcohol, was added 10 g 4(5)-phenyl-2-mercaptoimidazole. After the latter had dissolved, 11.3 g diethylacetal of bromoacetaldehyde was added and the solution boiled 11 hours. The mixture was then cooled and filtered from sodium bromide, and the solvent was taken off in vacuum. The oily residue was dissolved in chloroform and the solution washed with water and dried with magnesium sulfate. After removal of the chloroform in vacuum, the substance was dried in a desiccator. Yield 16.3 g (98.2%) of the diethylacetal of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde. A colorless, viscous oil, soluble in organic solvents and mineral acids, insoluble in water; it decomposes when an attempt is made to distill it in vacuum.

Picrate: yellow crystals (from alcohol) with m.p. 126-127°.

Found %: C 48.43; H 4.62; N 13.58; S 5.89. $C_{21}H_{23}O_9N_5S$. Calculated %: C 48.34; H 4.44; N 13.43; S 6.15**

The dimethylacetal of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde (I) was similarly prepared from the dimethylacetal of bromoacetaldehyde in methyl alcohol. A colorless, viscous oil, resembling (II) in solubility.

3-Ethoxy-6-phenylimidazo-(2,1-b)-thiazoline (IV). A solution of 8.9 g diethylacetal of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde in 20 ml phosphorus oxychloride was boiled for $1^1/_2$ hours; the phosphorus oxychloride was then distilled off in vacuum. After cooling of the oily residue, water was added and the mixture neutralized with sodium bicarbonate solution. The oily substance that separated out was extracted with chloroform, the solution was dried with magnesium sulfate and the solvent was removed in vacuum. The residual oil crystallized on cooling. The crystals were washed on the filter with a small quantity of ether and dried. Yield 6.5 g (75.1%) of substance with m.p. 114-116°. The 3-ethoxy-6-phenylimidazo-(2,1-b)-thiazoline was recrystallized from alcohol for analysis. Colorless prisms with m.p. 122°, soluble in organic solvents and solutions of mineral acids, insoluble in water, ligroin and caustic alkali solution.

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* Tests were undertaken by A. A. Mikerina under the direction of G. N. Pershin.

** All analyses were carried out in the microanalytical laboratory of our institute.

Found %: C 63.20; H 5.76; N 11.25; S 12.72. $C_{13}H_{14}ON_2S$. Calculated %: C 63.37; H 5.73; N 11.38; S 13.02.

Picrate: yellow needles (from alcohol) with m.p. 197-198° (with decomp.).

Found %: N 14.66. $C_{19}H_{17}O_8N_5S$. Calculated %: N 14.73.

3-Methoxy-6-phenylimidazo-(2,1-b)-thiazoline (III) was similarly prepared from the dimethylacetal of 4 (5)-phenylimidazolyl-2-mercaptoacetaldehyde (I). After the chloroform had distilled off,, the substance did not crystallize. It was converted to the hydrochloride in ethereal solution by the action of an alcoholic solution of hydrogen chloride. After crystallization from alcohol the hydrochloride had m.p. 141-142° (with decomp.).

Found %: C 50.13; H 5.39; N 10.07; S 11.06; Cl 12.50; H_2O 6.77. $C_{13}H_{13}ON_2SCl \cdot H_2O$. Calculated %: C 50.24; H 5.27; N 9.76; S 11.18; Cl 12.37; H_2O 6.28.

The base (III) was obtained from the alcoholic solution of the hydrochloride by the action of sodium bicarbonate. For analysis it was first recrystallized from a mixture of carbon tetrachloride and ligroine and then from a mixture of anhydrous ethyl alcohol and ligroin. Colorless crystals with m.p. 71.5-72.5°, readily soluble in organic solvents and solutions of mineral acids, insoluble in water, ligroin and caustic alkali solution.

Found %: C 62.11; H 5.30; N 11.70; S 13.68. $C_{12}H_{12}ON_2S$. Calculated %: C 62.01; H 5.21; N 12.06; S 13.80.

Picrate: yellow needles from alcohol, m.p. 172-173° (with decomp.).

Found %: N 14.98. $C_{18}H_{15}O_8N_5S$. Calculated %: N 15.18.

3-Hydroxy-6-phenylimidazo-(2,1-b)-thiazoline (V). a) A mixture of 8.7 g α,β-dibromoethyl ether and 70 ml water was boiled several minutes until a homogeneous solution had been formed. To the hot solution was then added 6.6 g 4(5)-phenyl-2-mercaptoimidazole and the resultant suspension was boiled for 1 hour (until the substance had dissolved completely). The solution was cooled and neutralized with sodium bicarbonate solution; the precipitate was then filtered, washed with water and dried. Yield 8 g with m.p. 146-149° (with decomp.). The 3-hydroxy-6-phenylimidazo-(2,1-b)-thiazoline was purified for analysis by recrystallization successively from alcohol, acetone, ethyl acetate and again from alcohol. Colorless needles with m.p. 160-161° (with decomp.), soluble in the majority of organic solvents and in solutions of mineral acids, sparingly soluble in carbon tetrachloride, benzene and ether, insoluble in ligroin, caustic alkali solution and water.

Found %: C 60.39; H 4.43; N 12.76; S 14.49. $C_{11}H_{10}ON_2S$. Calculated %: C 60.51; H 4.62; N 12.84; S 14.69.

Hydrochloride: colorless crystals (from alcohol) with m.p. 163-165° (with decomp.).

Found %: Cl 13.96. $C_{11}H_{11}ON_2SCl$. Calculated %: Cl 13.93.

Picrate: yellow prisms (from alcohol) with m.p. 145-146° (with decomp.), crystallizing with two molecules of water which are lost at above 100°.

Found %: C 42.45; H 3.50; N 14.72. $C_{17}H_{13}O_8N_5S \cdot 2H_2O$. Calculated %: C 42.22; H 3.55; N 14.30. After drying at 110-115° found %: C 45.46; H 2.91. $C_{17}H_{13}O_8N_5S$. Calculated %: C 45.61; H 2.92.

b) To a suspension of 6.5 g 4(5)-phenyl-2-mercaptoimidazole in 65 ml anhydrous benzene was added 8.6 g α,β-dibromoethyl ether; the mixture was boiled $1^1/_4$ hours. The benzene was then removed in vacuum, and the residue was dissolved in water and neutralized with sodium bicarbonate solution; the resultant white precipitate was filtered, washed with water and dried. Yield 8.1 g substance with m.p. 124-128° (with decomp.); after recrystallization from alcohol, (V) was obtained with m.p. 160-161° (with decomp.). A mixture with the substance obtained by method (a) melted at 160-161°.

c) A solution of 2 g of the diethylacetal of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde in 10 ml 38% hydrochloric acid was boiled 1 hour 20 minutes, after which it was cooled and 7 ml water was added. The precipitate was filtered and dried. Yield 1.2 g substance with m.p. 158-161° (with decomp.); recrystallization from alcohol gave colorless crystals with m.p. 163-165° (with decomp.). A mixture with the hydrochloride of (V) melted at 163-165° (with decomp.). After separation of the hydrochloride, the hydrochloric acid mother liquor was neutralized with sodium bicarbonate solution, and the resultant precipitate was filtered and dried. Yield 0.3 g substance with m.p. 145-150° (with decomp.); recrystallization from alcohol gave colorless needles with m.p. 160-161° (with decomp.). A mixture with (V) obtained by method (a) melted at 160-161° (with decomp.). Total yield 85%.

d) 15-20 ml alcoholic solution of hydrogen chloride was added to 6 g of the diethylacetal of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde. After standing at room temperature for over 24 hours, a crystalline precipitate was formed and was filtered off and recrystallized from alcohol. A mixture of this hydrochloride (m.p. 163-165° with decomp.) with the hydrochloride of (V) melted at 163-165° (with decomp.).

Under similar conditions the hydrochloride of (V) with m.p. 163-165° (with decomp.) was prepared from the dimethylacetal of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde.

3-Hydroxy-6-p-nitrophenylimidazol-(2,1-b)-thiazoline. To a suspension of 6 g 4(5)-p-nitrophenyl-2-mercaptoimidazole in 50 ml water was added 6.3 g α,β-dibromodiethyl ether, and the mixture was boiled 3 hours. The solution was cooled and neutralized with sodium bicarbonate solution; the yellow precipitate was filtered off, washed with water and dried. Yield 6.9 g (96.5%) 3-hydroxy-6-p-nitrophenylimidazo-(2,1-b)-thiazoline. Yellow crystals (from acetone) with m.p. 203-204° (with decomp.), sparingly soluble in most organic solvents, insoluble in ether, water and caustic alkali solution.

Found %: C 50.13; H 3.48; N 15.87; S 11.90. $C_{11}H_9O_3N_3S$. Calculated %: C 50.16; H 3.45; N 15.97; S 12.22.

6-Phenylimidazo-(2,1-b)-thiazole (VI). a) A solution of 2 g 2-aminothiazole and 3.97 g α-bromoacetophenone in 45 ml alcohol was boiled for $1^1/_2$ hours. The precipitate (which came down on cooling) was filtered and dried. A further small quantity of the substance was obtained by evaporation of the mother liquor to a small volume and addition of ether. Yield 5.1 g (90.9%) of the hydrobromide of 6-phenylimidazo-(2,1-b)-thiazole with m.p. 110-113°; recrystallization from acetone gave colorless needles with m.p. 114-116°, soluble in water, alcohol and acetone.

Found %: Br 28.11. $C_{11}H_9N_2SBr$. Calculated %: Br 28.43.

Addition of sodium bicarbonate solution to the aqueous solution of the hydrobromide yielded the base – 6-phenylimidazo-(2,1-b)-thiazole – in the form of colorless needles (from aqueous alcohol) with m.p. 146-146.5°, soluble in most organic solvents and in solutions of mineral acids, insoluble in ligroin, water and caustic alkali solution.

Found %: C 66.05; H 3.90; N 13.86; S 15.70. $C_{11}H_8N_2S$. Calculated %: C 65.96; H 4.02; N 13.99; S 16.02.

Hydrochloride: colorless needles (from alcohol) with m.p. 153-154°.

Found %: Cl 14.47. $C_{11}H_9N_2SCl$. Calculated %: Cl 14.99.

Sulfate: colorless prisms from alcohol, with m.p. 210-211°, sparingly soluble in water and alcohol; crystallizes with one molecule of crystal water.

Found : S (total) 19.98; S (ionic) 10.08. $C_{11}H_{10}O_4N_2S_2 \cdot H_2O$. Calculated %: S (total) 20.27; S (ionic) 10.13.

Picrate: yellow plates (from alcohol) with m.p. 223-223.5°.

Found %: N 15.91. $C_{17}H_{11}O_7N_5S$. Calculated %: N 16.32.

b) A solution of 1.4 g diethylacetal of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde in 6.5 ml 95% sulfuric acid was heated at 45-50° for 30 minutes; it was then poured into 12-15 ml water and heated on a boiling water bath for 1 hour. The brown solution was cooled, neutralized with sodium carbonate solution and extracted with chloroform. The chloroform solution was dried with magnesium sulfate and evaporated to dryness in vacuum; the oily residue was dissolved in alcohol and added to an aqueous solution of picric acid. Yield 0.15 g; recrystallization from alcohol gave yellow plates with m.p. 223°. A mixture with the picrate (VI) melted at 223°

c) A solution of 1 g 3-hydroxy-6-phenylimidazo-(2,1-b)-thiazoline in 6 ml 95.6% sulfuric acid was heated at 30° for 7-10 minutes, after which it was left for several hours at room temperature. The brown solution was run into 20 ml water and neutralized with sodium hydroxide; the resultant precipitate was filtered, washed with water and dried. Yield 0.6 g (74.1%) substance with m.p. 135-138°; recrystallization from aqueous alcohol gave colorless needles with m.p. 146-146.5°. A mixture with (VI) melted at 146-146.5°. A mixture with the original substance (m.p. 160-161°) melted at 124-127°.

d) To 0.65 g 3-hydroxy-6-phenylimidazo-(2,1-b)-thiazole was added 3 ml phosphorus oxychloride; heat was developed. The solution was heated at the boil for 10 minutes, cooled, poured into iced water and neutralized with sodium hydroxide solution. The precipitate was then filtered off, washed with water and dried. Yield 0.4 g (67.8%) of (VI); recrystallization from aqueous alcohol gave colorless needles with m.p. 146-146.5°.

e) A solution of 0.1 g 3-methoxy-6-phenylimidazo-(2,1-b)-thiazoline in 3 ml 95.6% sulfuric acid was heated at 30° for 30 minutes, after which it was worked up as in the preceding experiment. Recrystallization from aqueous alcohol gave (VI) with m.p. 146-146.5°.

f) A solution of 0.6 g 3-ethoxy-6-phenylimidazo-(2,1-b)-thiazoline in 4 ml 92% sulfuric acid was heated to 35° and left overnight. It was then poured into 10 ml cold water. The precipitated sulfate of (VI) was filtered off and decomposed with sodium carbonate in aqueous solution. Yield 0.48 g (98%) of (VI) which had m.p. 146° without recrystallization.

6-p-Nitrophenylimidazo-(2,1-b)-thiazole. A solution of 3 g 3-hydroxy-6-p-nitrophenylimidazo-(2,1-b)-thiazoline in 50 ml phosphorus oxychloride was boiled for 2 hours; the phosphorus oxychloride was then distilled off in vacuum; water was added to the cooled residue and then sodium carbonate solution until the reaction was alkaline. The yellow precipitate was filtered off, washed with water and dried. Yield 2.7 g (98.4%) of substance with m.p. 275-277°; recrystallization from glacial acetic acid gave yellow needles with m.p. 283-284°; difficultly soluble in most organic solvents, insoluble in water and caustic alkali solution. A mixed specimen with 6-p-nitrophenylimidazo-(2,1-b)-thiazole (m.p. 283-284°), prepared from 2-aminothiazole and α-bromo-p-nitroacetophenone by the method of Matsukawa and Bann [7], melted at 283-284°.

Found %: N 17.07. $C_{11}H_7O_2N_3S$. Calculated %: N 17.14.

6-p-Sulfophenylimidazo-(2,1-b)-thiazole (VII). a) To 3.5 ml 95.6% sulfuric acid was added 0.3 g of the hydrochloride of 3-methoxy-6-phenylimidazo-(2,1-b)-thiazoline, and the solution was heated on a boiling water bath for 30 minutes. Hydrogen chloride was evolved at the start of heating. The brown solution was cooled and poured into 15-20 ml iced water; the precipitate was then filtered, washed with acetone and dried. Yield 0.22 g (79.7%) of 6-p-sulfophenylimidazo-(2,1-b)-thiazole; colorless, spindle-shaped crystals (from water), not melting at 360°, insoluble in organic solvents and mineral acids, difficultly soluble in water. The compound crystallizes with one molecule of crystal water which it loses at above 100°.

Found %: C 44.47; H 3.44; N 9.39; S 21.69; H_2O 6.07. $C_{11}H_8O_3N_2S_2 \cdot H_2O$. Calculated %: C 44.26; H 3.38; N 9.39; S 21.50; H_2O 6.23.

b) A solution of 0.5 g 3-ethoxy-6-phenylimidazo-(2,1-b)-thiazoline in 5 ml 95% sulfuric acid was heated on a boiling water bath for 1 hour, after which it was worked up as in the preceding experiment. Yield 0.46 g of (VII) (77%).

c) A solution of 1.7 g 3-hydroxy-6-phenylimidazo-(2,1-b)-thiazoline in 11 ml 95.6% sulfuric acid was heated on a boiling water bath for 30 minutes and then poured into 25 ml water; the resultant precipitate was filtered off, washed with water and dried. Yield 2.1 g substance which was put into a solution of sodium bicarbonate (10 ml). The insoluble portion was filtered off, washed with water and dried. Yield 0.1 g substance with m.p. (from alcohol) 146-146.5°. A mixed specimen with the starting substance (m.p. 160-161°) melted at 139-143°. A mixed specimen with (VI) (m.p. 146-146.5°) melted at 146-146.5°. The bicarbonate solution was neutralized with excess of concentrated hydrochloric acid; the white crystalline precipitate was filtered off, washed with acetone and dried. Yield 1.95 g (84.8%) of (VII).

d) A solution of 0.16 g 6-phenylimidazo-(2,1-b)-thiazole in 4 ml 95.6% sulfuric acid was heated on a boiling water bath for 30 minutes, after which it was worked up as in experiment (a). Yield 0.2 g (94.4%) of (VII).

SUMMARY

1. The action of bromoacetaldehyde on 4(5)-phenyl- and 4(5)-p-nitrophenyl-2-mercaptoimidazoles was studied.

2. The transformation of imidazolyl-2-mercaptoacetaldehydes and of their acetals into derivatives of 3-hydroximidazo-(2,1-b)-thiazoline, and the transformation of the acetals into imidazo-(2,1-b)-thiazoles were investigated.

3. A series of derivatives of 4(5)-phenylimidazolyl-2-mercaptoacetaldehyde, 3-hydroximidazo-(2,1-b)-thiazoline and imidazo-(2,1-b)-thiazole was synthesized.

4. A new mechanism of the closure of the thiazole ring was proposed on the basis of a study of the structure of the intermediate products during synthesis of imidazo-(2,1-b)-thiazoles.

LITERATURE CITED

[1] E. Ochiai, Ber. 69, 1650 (1936).

[2] E. Ochiai, and T. Y. Hou, J. Pharm. Soc. 58, 33(Japan, 1938); Chem. Zentr. 1938, II, 859.

[3] P. M. Kochergin and M. N. Shchukina, J. Gen. Chem. 26, 458 (1956). (T.p. 483). •

[4] P. M. Kochergin and M. N. Shchukina, J. Gen. Chem. 25, 2182 (1955). (T.p. 2145).•

[5] P. M. Kochergin, J. Gen. Chem. 26, 2493 (1956).

[6] P. M. Kochergin and M. N. Shchukina, J. Gen. Chem. 26, 1723 (1956) (T.p. 1933).•

[7] T. Matsukawa and S. Ban, J. Pharm. Soc. 71, 756 (Japan,1951); C. A. 46, 8094 (1952).

Received October 25, 1955

S. Ordzhonikidze Institute of Pharmaceutical
Chemical Research

• T.p. = C. B. Translation pagination.

INVESTIGATIONS IN THE IMIDAZOLE SERIES

VII. THE ACTION OF ACETIC ANHYDRIDE ON 2-β-KETOALKYL(ARYL)-MERCAPTOIMIDAZOLES

P. M. Kochergin

2-β-Ketoalkyl(aryl)-mercaptoimidazoles can split off a molecule of water when their hydrochlorides are boiled in butyl alcohol [1] or heated with phosphorus oxychloride [2-5] or with hydrochloric [1], sulfuric [5-7], phosphoric [4] or acetic [4, 6] acids. They are transformed in this way into derivatives of imidazo-(2,1-b)-thiazole. It was also of interest to study the dehydrating action of acetic anhydride on these compounds.

Ochiai [2] reacted acetic anhydride with 4(5)-methyl-5(4)-carbethyoxy-2-acetonyl-mercaptoimidazole in presence of anhydrous sodium acetate and obtained a substance to which he assigned the structure of 2-acetyl-3,6-dimethyl-5-carbethoxyimidazo-(2,1-b)-thiazole. The author did not isolate the intermediate product in this reaction – 1-acetyl-4-methyl-5-carbethoxy-2-acetonyl-mercaptoimidazole – so that in spite of the weighty theoretical arguments the mechanism of this reaction has remained uncertain.

The present work established that the action of acetic anhydride on 2-β-ketoalkyl(aryl)-mercaptoimidazoles is markedly different from that of the reagents cited above. The difference is that the primary action of acetic anhydride is not dehydration but acetylation, N-acetyl derivatives of 2-β-ketoalkyl(aryl)-mercaptoimidazoles being formed. Thus, on boiling the previously described [1] S-acetonyl-, methylacetonyl-, phenacyl- and cyclohexanonyl- derivatives of 4(5)-phenyl-2-mercaptoimidazole, as well as the S-acetonyl derivative of 4(5)-p-nitrophenyl-2-mercaptoimidazole, with acetic anhydride for 5-30 minutes, we obtained good yields (78-99%) of the corresponding 1-acetyl-5-phenyl(p-nitrophenyl)-2-β-ketoalkyl(aryl)-mercaptoimidazoles (I, II, III, VI and VII; Table 1). These compounds crystallize nicely from alcohol or glacial acetic acid; they hydrolyze with facility in hydrochloric acid solution, forming the hydrochlorides of the original 2-β-ketoalkyl (aryl)-mercaptoimidazoles.

N-Acetyl derivatives of 2-β-ketoalkyl(aryl)-mercaptoimidazoles containing a methylene group between the carbonyl group and the sulfur atom undergo cleavage of water at the expense of the hydrogen atoms of the methylene group and the oxygen of the N-acetyl group, forming 3-methylimidazo-(2,1-b)-thiazolyl-2-alkyl-(aryl)-ketones. This reaction goes with facility when 1-acetyl-2-β-ketoalkyl(aryl)-mercaptoimidazoles are boiled in acetic anhydride in presence of anhydrous sodium acetate. Thus, from 2-acetonylmercapto- and 2-phenacylmercapto-1-acetyl-5-phenylimidazoles (I and III; Table 1) we obtained compounds (I and II; Table 2).

As was first shown by Ochiai [2], 2-acyl-3-methylimidazo-(2,1-b)-thiazoles can also be prepared directly from 2-β-ketoalkyl(aryl)-mercaptoimidazoles by heating the latter with acetic anhydride and anhydrous sodium acetate without isolation of the intermediate N-acetyl derivatives of 2-β-ketoalkyl(aryl)-mercaptoimidazoles. We prepared compounds I and V (Table 2) from 4(5)-phenyl- and 4(5)-p-nitrophenyl-2-acetonyl-mercaptoimidazoles [1]. This closure of the thiazole ring takes place readily in the case of 4(5)-phenyl-2-nitrophenacyl-mercaptoimidazoles on boiling with acetic anhydride even in the absence of sodium acetate. The corresponding 1-acetyl-5-phenyl-2-nitrophenacyl-mercaptoimidazoles (IV and V; Table 1) together with products of their further transformation – 2-nitrobenzoyl-3-methyl-5-phenylimidazo-(2,1-b)-thiazoles (III and IV; Table 2) – could be isolated only by brief (3-5 minutes) heating of 4(5)-phenyl-2-nitrophenacyl-mercaptoimidazoles [1] with acetic anhydride.

On the basis of the results described above, the following mechanism of the action of acetic anhydride on 2-β-ketoalky(aryl)-mercaptoimidazoles is proposed [see top of p. 3246].

It should be noted that this characteristic closure of the thiazole ring has not previously been observed in the case of simple derivatives of thiazole not condensed with other rings.

Since the 4- and 5-positions in derivatives of imidazole with a free imino group are equivalent, two isomers could be theoretically formed both in the acetylation and alkylation of 4(5)-substituted 2-β-ketoalkyl (aryl)-mercaptoimidazoles; in the present case the isomers would be 4-phenyl(or p-nitrophenyl)-and 5-phenyl-

TABLE 1

1-Acetyl-5-phenyl(p-nitrophenyl)-2-β-ketoalkyl(aryl)-mercaptoimidazoles

No.	X	R	Yield	Color and form of crystals*	Melting point	Empirical formula	Calculated (in %)				Found** (in %)			
							C	H	N	S	C	H	N	S
(I)	H	CH_2COCH_3	96	Colorless needles	158—159°	$C_{14}H_{14}O_2N_2S$	—	—	10.21	—	—	—	10.09	—
(II)	H	$CH(CH_3)COCH_3$	99.7	Colorless needles	152—154	$C_{15}H_{16}O_2N_2S$	62.46	5.60	9.72	11.13	62.50	5.40	9.86	11.07
(III)	H	$CH_2COC_6H_5$	94.6	Colorless needles	171—171.5	$C_{19}H_{16}O_2N_2S$	67.81	4.80	8.33	9.54	67.62	4.86	8.66	9.55
(IV)	H	$CH_2COC_6H_4NO_2$-p	76	Yellow needles	169—170	$C_{19}H_{15}O_4N_3S$	—	—	11.02	—	—	—	10.97	—
(V)	H	$CH_2COC_6H_4NO_2$-m	—	Yellow needles	161—162	$C_{19}H_{15}O_4N_3S$	—	—	11.02	—	—	—	10.92	—
(VI)	H	C_6H_9O	78.1	Colorless needles	156—157	$C_{17}H_{18}O_2N_2S$	64.93	5.77	8.91	10.20	65.15	5.92	9.20	9.88
(VII)	NO_2	CH_2COCH_3	95.7	Yellow, thread-like crystals	182—183	$C_{14}H_{13}O_4N_3S$	—	—	13.17	—	—	—	13.12	—

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* Compounds I to VI were recrystallized from alcohol, VII from glacial acetic acid.

** All analyses of compounds listed in Tables 1 and 2 were carried out in the microanalytical laboratory of our institute.

TABLE 2

3-Methyl-imidazo-(2,1-b)-thiazolyl-2-alkyl(aryl)-ketones

№	R¹	R²	R³	R⁴	Yield (in %)	Color and form of crystals*	Melting point	Empirical formulas	Calculated (in %)				Found (in %)			
									C	H	N	S	C	H	N	S
(I)	$COCH_3$	CH_3	C_6H_5	H	98.6	Colorless needles	150—151°	$C_{14}H_{12}ON_2S$	65.58	4.72	10.93	12.51	65.73	4.74	10.83	12.82
(II)	COC_6H_5	CH_3	C_6H_5	H	—	Colorless plates	227—228	$C_{19}H_{14}ON_2S$	71.65	4 44	8.80	10.08	71.52	4.38	8.66	9.86
(III)	$COC_6H_4NO_2$-*n*	CH_3	C_6H_5	H	—	Yellow needles	190	$C_{19}H_{13}O_3N_3S$	62.78	3.61	—	8.81	62.80	3.74	—	8.82
(IV)	$COC_6H_4NO_2$-*м*	CH_3	C_6H_5	H	89.2	Yellow plates	144—145	$C_{19}H_{13}O_3N_3S$	62.78	3.61	11.57	8.81	62.69	3.61	11.27	8.68
(V)	$COCH_3$	CH_3	$C_6H_4NO_2$-*n*	H	76.5	Yellow needles	186—187	$C_{14}H_{11}O_3N_3S$	55.78	3.68	13.95	10.64	56.13	3.63	13.97	10.78
(VI)	$COCH_3$	CH_3	H	C_6H_5	74.5	Colorless plates	203—203.5	$C_{14}H_{12}ON_2S$	65.58	4.72	10.93	12.51	65.44	4.58	11.11	12.09
(VII)	$COCH_3$	CH_3	H	$C_6H_4NO_2$-*n*	—	Yellow prisms	281—281.5	$C_{14}H_{11}O_3N_3S$	55.78	3.68	13.95	10.64	56.09	3.69	13.63	10.62

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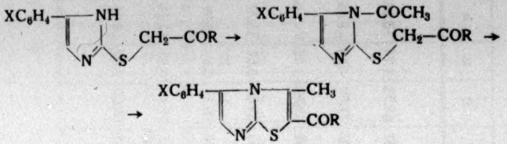
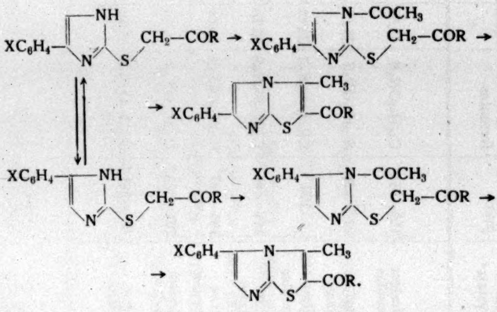
* Compounds I to IV and VI were recrystallized from alcohol, V and VII from glacial acetic acid.

(p-nitrophenyl)-1-acetyl-2-β-ketoalkyl(aryl)-mercaptoimidszoles. Subsequently, each of these isomers could give, respectively, 6-phenyl(p-nitrophenyl)- and 5-phenyl-(p-nitrophenyl)-2-acyl-3-methylimidazo-2,1-b)-thiazole.



(p-nitrophenyl)-1-acetyl-2-β-ketoalkyl(aryl)-mercaptoimidazoles. Subsequently, each of these isomers could give, respectively, 6-phenyl(p-nitrophenyl)- and 5-phenyl-(p-nitrophenyl)-2-acyl-3-methylimidazo-(2,1-b)-thiazole.

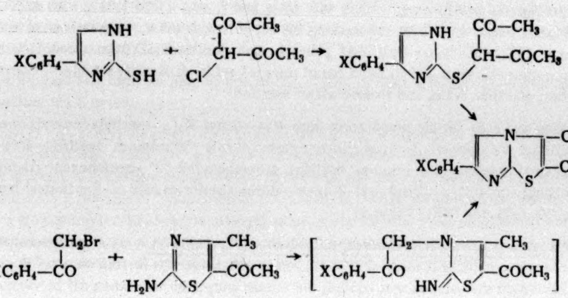


In all cases we isolated only one N-acetyl derivative of 2-β-ketoalkyl(aryl)-mercaptoimidazoles or one imidazo-(2,1-b)-thiazolyl-2-alkyl(aryl)-ketone, except in experiments when a mixture of the first and second was obtained

A direct proof of the structure of the synthesized N-acetyl compounds is extremely difficult. The problem is to establish whether they have the structure of 4-phenyl(p-nitrophenyl)- or of 5-phenyl(p-nitrophenyl)-1-acetyl-2-β-ketoalkyl(aryl)-mercaptoimidazoles. Reductive cleavage of imidazole derivatives with tin chloride in hydrochloric acid [8,9], which is used for verification of the structure of 1,4- or 1,5-dialkyl(alkylaryl, etc)-substituted imidazoles, is not easily realizable in the present case because this proof can only be carried out after preliminary reduction of 1-acetyl-4(or 5)-arylimidazoles to 1-ethyl-4(or 5)-arylimidazoles. Since the N-acetyl group is easily saponified in acid and alkaline media, while the imidazole ring is readily attacked by strong reducing agents, it is difficult to find a reagent and to select the conditions that would ensure reduction of the acetyl group to ethyl without appreciable hydrolysis and cleavage of the imidazole ring. And even if this could be successfully carried out, the further proof of the position of the aryl group by the above-mentioned method would meet with considerable experimental difficulties. Equally difficult would also be the direct proof of the position of the aryl group in 2-acyl-3-methyl-5-arylimidazo-(2,1-b)-thiazoles.

It was subsequently established beyond doubt, by transformation of N-acetyl derivatives of 2-β-ketoalkyl (aryl)-mercaptoimidazoles into 3-methylimidazo-(2,1-b)-thiazolyl-2-alkyl(aryl)-ketones, that the former compounds are 1-acetyl-5-phenyl(p-nitrophenyl)-2-β-ketoalkyl(aryl)-mercaptoimidazoles, while the products of their dehydration are 2-acyl-3-methyl-5-phenyl(p-nitrophenyl)-imidazo-(2,1-b)-thiazoles. The proof was carried out for 5-phenyl- and 5-p-nitrophenyl-1-acetyl-2-acetonylmercaptoimidazoles (I and VII; Table 1) and the derived imidazo-(2,1-b)-thiazolyl-2-methylketones (I and V; Table 2). We argued that if the

N-acetyl compounds had the structure of 4-phenyl- and 4-p-nitrophenyl-1-acetyl-2-acetonylmercaptoimidazoles, then after cleavage of a molecule of water they should give 6-phenyl- and 6-p-nitrophenyl-2-acetyl-3-methylimidazo-(2,1-b)-thiazoles. We obtained the latter compounds (VI and VII; Table 2) from 4(5)-phenyl- and 4(5)-nitrophenyl-2-mercaptoimidazoles [10] and 3-chloro-2,4-pentanedione [11] followed by cyclization of the 4(5)-phenyl- and 4(5)-p-nitrophenyl-2-(α-acetylacetonyl)-mercaptoimidazoles by the usual methods – in the former case by boiling in butyl alcohol and in the latter case by boiling in phosphorus oxychloride. In these cases, as was previously demonstrated for analogous compounds [1,4,5], the phenyl or p-nitrophenyl group is always attached in the 6-position of the imidazo-(2,1-b)-thiazole bicycle. One of these compounds – 2-acetyl-3-methyl-6-p-nitrophenylimidazo-(2,1-b)-thiazole (VI; Table 2) – was also obtained by reverse synthesis (which confirms its structure) from 4-methyl-5-acetyl-2-aminothiazole [12] and α-bromo-p-nitroacetophenone. The reaction did not go with α-bromoacetophenone, just as in the case of 4-phenyl-2-aminothiazole [4], and 2-acetyl-3-methyl-6-phenylimidazo-(2,1-b)-thiazole could not be synthesized by this method.



The prepared 6-phenyl- and 6-p-nitrophenyl-2-acetyl-3-methylimidazo-(2,1-b)-thiazoles (VI and VII, Table 2) were found to be not identical with the isomeric compounds (I and V; Table 2) synthesized from 4(5)-phenyl- and 4(5)-p-nitrophenyl-2-acetonylmercaptoimidazoles through their N-acetyl derivatives.

It follows that compounds prepared by dehydration of N-acetyl derivatives of phenyl- and p-nitrophenyl-2-acetonylmercaptoimidazoles contain the aryl group not in the 6- but in the 5-position of the imidazo-(2,1-b)-thiazole bicycle, and the corresponding original N-acetyl compounds are 1-acetyl-5-aryl-2-acetonylmercaptoimidazoles.

We did not prove the structure of other N-acetyl derivatives of 2-β-ketoalkyl(aryl)-mercaptoimidazoles (II-VI; Table 1) and of the derived imidazo-(2,1-b)-thiazolyl-2-alkyl(aryl)-ketones (II-IV; Table 2), but by analogy we may assume that the former are 1-acetyl-5-phenyl-2-β-ketoalkyl(aryl)-mercaptoimidazoles and the latter are 2-acyl-3-methyl-5-phenylimidazo-(2,1-b)-thiazoles.

Consequently, the action of acetic anhydride on 2-β-ketoalkyl(aryl)-mercaptoimidazoles proved to be interesting not only theoretically but also from the practical aspect, since a new method of preparation of derivatives of imidazo-(2,1-b)-thiazole is now available. It is highly probable that with the application of other carboxylic acid anhydrides or chlorides for acylation, we could prepare various N-acyl-2-β-ketoalkyl-(aryl)-mercaptoimidazoles, from which in turn could be derived imidazo-(2,1-b)-thiazoles with a diversity of substituents in the 2-, 3-, 5- and 6-positions.

Theoretical interest is attached not only to the unusual method of closure of the thiazole ring but also to the reaction of acetylation of 4(5)-aryl-2-mercapto-substituted imidazoles, leading to formation of 1-acetyl-5-aryl isomers, whereas in the alkylation of 4(5)-aryl(or alkyl)-imidazoles [9,13,14] and 4(5)-aryl-2-alkylmercaptoimidazoles [15] the sole or the predominating products are 1-alkyl-4-aryl(alkyl)-isomers. Thus, the directive influence of aryl (and possibly also of alkyl) radicals in the acetylation of 4(5)-substituted imidazoles is not identical with the influence of these radicals during alkylation. In the light of these facts it is highly probable that the compound obtained by Ochiai [2] is not 2-acetyl-3,6-dimethyl-5-carbethoxyimidazo-(2,1-b)-thiazole but 2-acetyl-3,5-dimethyl-6-carbethoxyimidazo-(2,1-b)-thiazole , while the compound prepared by Bojer and Straw [16] is not 1-acetyl-2-benzoyl-4-phenylimidazole but 1-acetyl-2-benzoyl-5-phenylimidazole.

Some of the compounds that we synthesized (II, III and VI, Table I, and III and IV, Table 2) were tested for antibacterial activity (range of 16 varieties of organisms).* They were found to be almost entirely devoid of antimicrobial activity.

We are extremely grateful to M. N. Shchukina for making it possible to carry out this investigation.

EXPERIMENTAL

1-Acetyl-5-phenyl-2-acetonylmercaptoimidazole. (I, Table 1). A mixture of 1.25 g 4(5)-phenyl-2-acetonylmercaptoimidazole and 6 ml acetic anhydride was boiled for 5-7 minutes, after which the solution was cooled and the precipitate was filtered, washed with ether and dried. Yield 1.21 g with m.p. 157-158°. By evaporating the mother liquor to dryness and washing the crystals with ether, we obtained a further 0.2 g of the substance with m.p. 156-157°. Total yield 1.41 g (96%). Colorless needles (from alcohol) with m.p. 158-159°, soluble in most organic solvents and in solutions of mineral acids, difficultly soluble in carbon tetrachloride, insoluble in ether, gasoline, water and caustic alkali solution.

The same method was used for the preparation from 4(5)-phenyl-2-(α-methylacetonyl)-mercaptoimidazole (30 minutes' boiling), 4(5)-phenyl-2-phenacylmercaptoimidazole (30 minutes' boiling), 4(5)-phenyl-2-m-nitrophenacylmercaptoimidazole (3-5 minutes' boiling), 4(5)-phenyl-2-(2'-cyclohexanoyl)-mercaptoimidazole (30 minutes' boiling) and 4(5)-p-nitrophenyl-2-acetonylmercaptoimidazole (4-5 minutes' boiling) of respectively (II), (III), (V), (VI) and (VII) (Table 1).

1-Acetyl-5-phenyl-2-p-nitrophenacylmercaptoimidazole (IV, Table 1). a) A mixture of 0.7 g 4(5)-phenyl-2-p-nitrophenacylmercaptoimidazole and 15 ml acetic anhydride was heated on a boiling water bath for 8-10 minutes, after which the solution was cooled, the acetic anhydride was taken off in vacuum, and the residue was washed with ether and dried. Yield 0.6 g (76%) of substance with m.p. 154-158°; recrystallization from alcohol gave yellow needles with m.p. 169-170°, soluble in most organic solvents, insoluble in water. A mixture with the original substance (m.p. 155°) melted at 169-170°.

b) A solution of 3.7 g 4(5)-phenyl-2-p-nitrophenacylmercaptoimidazole in 26 ml acetic anhydride was boiled for 5-7 minutes, after which the acetic anhydride was distilled off in vacuum; the viscous residue in the flask crystallized on washing with acetone; it was filtered and dried. Yield 1.4 g substance with m.p. 152-155°; recrystallization from alcohol gave 1-acetyl-5-phenyl-2-p-nitrophenacylmercaptomidazole; m.p. 169-170°. A mixed specimen with the substance obtained in experiment (a) melted at 169-170°.

An alcoholic solution of hydrogen chloride was added to the acetone mother liquor after separation of the 1-acetyl-5-phenyl-2-p-nitrophenacylmercaptoimidazole; the resultant precipitate was filtered and dried. Yield 0.6 g 2-p-nitrobenzoyl-3-methyl-5-phenylimidazo-(2,1-b)-thiazole (III, Table 2); recrystallization from alcohol gave yellow needles with m.p. 190°, soluble in organic solvents, insoluble in water. From a hot alcoholic solution of hydrogen chloride, this compound separates in the form of the base with m.p. 190°. A mixture with 1-acetyl-5-phenyl-2-p-nitrophenacylmercaptoimidazole (m.p. 169-170°) melted at 160-163°.

2-Acetyl-3-methyl-5-phenylimidazo-(2,1-b)-thiazole (I, Table 2). a) A mixture of 0.8 g 1-acetyl-5-phenyl-2-acetonylmercaptoimidazole (I, Table 2), 0.8 g anhydrous sodium acetate and 4.5 ml acetic anhydride was boiled for 30 minutes, after which the acetic anhydride was taken off in vacuum. The residue, which crystallized on cooling, was washed with water and dried. Yield 0.74 g (98.6%) of substance with m.p. 129-138°; recrystallization from alcohol gave colorless needles with m.p. 150-151°, soluble in most organic solvents and in hydrochloric acid, sparingly soluble in ether, insoluble in ligroin, water and caustic alkali solution. A mixture with the original substance (m.p. 158-159°) melted at 118-120°. The same method was applied to the preparation of II (Table 2) from III (Table 1) but with the difference that after the acetic anhydride had been distilled off, extraction of (II) was effected with chloroform and the solution was washed with water, dried with potassium carbonate and evaporated to dryness in vacuum.

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* Investigations were undertaken by S. N. Milovanova and A. A. Mikerina under the direction of G. N. Pershin.

b) A mixture of 1.55 g 4(5)-phenyl-2-acetonylmercaptoimidazole, 1.55 g anhydrous sodium acetate and 9 ml acetic anhydride was boiled for 30 minutes, after which the mixture was cooled and the precipitate was filtered, washed with a little ether and suspended in water. The insoluble precipitate was filtered, washed with water and dried. Yield 1.2 g substance with m.p. 143-145°. Evaporation of the acetic-ethereal mother liquor gave a further 0.45 g of this substance with m.p. 140-144°. Total yield 1.65 g (97%). Colorless needles (from alcohol) with m.p. 150-151°. A mixture with the substance prepared by method (a) melted at 150-151°.

The same method was applied to the preparation of (V, Table 2) from 4(5)-p-nitrophenyl-2-acetonylmercaptoimidazole; the product had m.p. 186-187°. A mixture of (V) with (VII, Table 1) (m.p. 182-183°) melted at 146-152°.

2-m-Nitrobenzoyl-3-methyl-5-phenylimidazo-(2,1-b)-thiazole (IV, Table 2). A mixture of 1 g 4(5)-phenyl-2-m-nitrophenacylmercaptoimidazole and 5 ml acetic anhydride was boiled for 30 minutes, after which the solution was cooled and the precipitate was filtered, washed with ether and dried. Yield 0.6 g substance with m.p. 143-144°. An additional 0.35 g of this substance was obtained by evaporating the mother liquor to dryness and washing the residue with ether. Total yield 0.95 g (89.2%). Yellow plates (from alcohol) with m.p. 144-145°, soluble in most organic solvents and in mineral acid solutions, insoluble in ether, water and caustic alkali solution. A mixture with (V, Table 1) (m.p. 161-162°) melted at 125-129°.

The same method was used for preparation of (III, Table 2) from 4(5)-phenyl-2-p-nitrophenacylmercaptoimidazole (boiling for 2 hours).

4(5)-Phenyl-2-(α-acetylacetonyl)-mercaptoimidazole. To a solution of 5 g 4(5)-phenyl-2-mercaptoimidazole in 75 ml alcohol was added 3.85 g 3-chloro-2,4-pentanedione and the mixture was boiled for 15 minutes, after which the solution was evaporated to dryness in vacuum and the crystalline residue was washed with ether and dried. Yield 8.75 g (99.2%) of hydrochloride (m.p. 148-151° with decomp.) from which, in aqueous solution, the base – 4(5)-phenyl-2-(α-acetylacetonyl)-mercaptoimidazole – was obtained by addition of sodium acetate. Colorless crystals with a pink tinge from alcohol, acetone or ethyl acetate, m.p. 135-136°, soluble in organic solvents and mineral acids, insoluble in water and caustic alkali solution.

Found %: C 61.50; H 5.35; N 10.12; S 11.51. $C_{14}H_{14}O_2N_2S$. Calculated %: C 61.27; H 5.15; N 10.22; S 11.69.

4(5)-p-Nitrophenyl-2-(α-acetylacetonyl)-mercaptoimidazole. 5.4 g 4(5)-p-nitrophenyl-2-mercaptoimidazole and 3.4 g 3-chloro-2,4-pentanedione were added to a solution prepared from 0.56 g metallic sodium and 75 ml alcohol, and the mixture was boiled for about an hour. The solution was filtered from sodium chloride, and cooled, and the precipitate was filtered and dried. Yield 2.2 g substance with m.p. 142-144°. Evaporation of the mother liquor to dryness and washing of the crystals with a little ether gave a further 5.1 g of the substance. Total yield 7.8 g (91%). Yellow crystals from ethyl acetate, m.p. 144-145°, soluble in most organic solvents, insoluble in ether, water and caustic alkali solution.

Found %: C 52.68; H 4.27; N 13.40; S 10.05. $C_{14}H_{13}O_4N_3S$. Calculated %: C 52.64; H 4.10; N 13.17; S 10.04.

2-Acetyl-3-methyl-6-phenylimidazo-(2,1-b)-thiazole (VI, Table 2). A solution of 2 g 4(5)-phenyl-2-(α-acetylacetonyl)-mercaptoimidazole hydrochloride in 10 ml butyl alcohol was boiled for an hour. The solution was cooled and the crystalline precipitate filtered, washed with a little acetone and then with ether and dried. Yield 1.4 g (74.5%) of hydrochloride (m.p. 232-234°) from which (in aqueous solution) the base – 2-acetyl-3-methyl-6-phenyl-imidazo-(2,1-b)-thiazole – was isolated by addition of sodium acetate. Colorless rectangular plates (from alcohol) with m.p. 203-203.5°. A mixture with 2-acetyl-3-methyl-5-phenylimidazo-(2,1-b)-thiazole (I, Table 2) (m.p. 150-151°) melted at 125-128°.

2-Acetyl-3-methyl-6-p-nitrophenylimidazo-(2,1-b)-thiazole (VII, Table 2). a) A solution of 2.7 g 4-(5)-p-nitrophenyl-2-(α-acetylacetonyl)-mercaptoimidazole in 40 ml phosphorus oxychloride was boiled for 30 minutes, after which the phosphorus oxychloride was distilled off in vacuum; water was added to the residue, followed by sodium bicarbonate solution until alkaline. The precipitate was filtered, washed with water and dried. Yield 2.5 g (98 %) 2-acetyl-3-methyl-6-p-nitrophenylimidazo-(2,1-b)-thiazole. Yellow prisms (from glacial acetic acid) with m.p. 281-281.5°, soluble in alcohol and other organic solvents, sparingly soluble in ether, insoluble in water and caustic alkali solution.

b) To a hot solution of 1.9 g 4-methyl-5-acetyl-2-aminothiazole in 250 ml alcohol was added 3 g of α-bromo-p-nitroacetophenone, and the mixture was boiled for 2 hours. The alcohol was then evaporated off and to the residue was added 25 ml glacial acetic acid, after which the solution was heated at the boil for an hour; it was then cooled, diluted with 25 ml acetone and cooled at -10°. The yellow precipitate was filtered off, washed with acetone and dried. Another small quantity of this substance was obtained by evaporation of the mother liquor. Yield 2.45 g (67%) of 2-acetyl-3-methyl-6-p-nitrophenyl-imidazo-(2,1-b)-thiazole; recrystallization from glacial acetic acid with additon of a little sodium acetate gave yellow prisms with m.p. 281-281.5°. A mixture with the substance prepared by method (a) melted at 281-281.5°.

SUMMARY

1. The action of acetic anhydride on 4(5)-phenyl- and 4(5)-p-nitrophenyl-2-β-ketoalkyl(aryl)-mercaptoimidazoles was studied.

2. A series of 1-acetyl-5-phenyl(p-nitrophenyl)-2-β-ketoalkyl(aryl)-mercaptoimidazoles was prepared and their structure established.

3. A series of 3-methyl-5-phenyl(p-nitrophenyl)- and 3-methyl-6-phenyl(p-nitrophenyl)-imidazo-(2,1-b)-thiazolyl-2-alkyl(aryl)-ketones was synthesized and their structure established.

LITERATURE CITED

[1] P. M. Kochergin and M. N. Shchukina, J. Gen. Chem. 26, 458 (1956). (T.p. 483).*

[2] E. Ochiai, Ber. 69, 1650 (1936).

[3] E. Ochiai and F. Y. Hou, J. Pharm. Soc. 58, 33 (Japan, 1938); Chem. Zentr. 1938, II, 859.

[4] P. M. Kochergin, J. Gen. Chem 26, 2493 (1956).

[5] P. M. Kochergin and M. N. Shchukina, J. Gen. Chem. 26, 2905,(1956) (T.p. 3233).*

[6] H. Andersag and K. Westphal, Ber. 70, 2035 (1937).

[7] P. M. Kochergin and M. N. Shchukina, J. Gen. Chem. 26, 1723 (1956). (T.p. 1933).*

[8] F. L. Pyman, J. Chem. Soc. 121, 2616 (1922).

[9] C. E. Hazeldine, F. L. Pyman and J. Winchester, J. Chem. Soc. 125, 1431 (1924).

[10] P. M. Kochergin and M. N. Shchukina, J. Gen. Chem. 25, 2182 (1955). (T.p. 2145).*

[11] E. R. Buchman and E. M. Richardson, J. Am. Chem. Soc. 67, 398 (1945).

[12] P. M. Kochergin, J. Gen. Chem. 26, 2897 (1956). (T.p. 3223).*

[13] F. L. Pyman, J. Chem. Soc 97, 1814 (1910).

[14] W. G. Forsyth and F. L. Pyman, J. Chem. Soc. 127, 573 (1925).

[15] R. M. Dodson and F. Ross, J. Am. Chem. Soc. 72, 1478 (1950).

[16] J. H. Bojer and D. Straw, J. Am. Chem. Soc. 74, 4506 (1952).

Received October 28, 1955

All-Union S. Ordzhonikidze Institute of
Pharmaceutical Chemical Research

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* T.p. = C. B. Translation pagination.

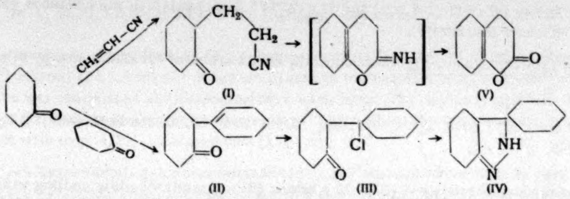
SYNTHESIS WITH THE HELP OF ACRYLONITRILE

XXIX. THE CYANOETHYLATION OF SOME KETONES

A. P. Terentyev, A. N. Kost, Yu. V. Saltykova and V. V. Ershov

Several papers have been published [1-3] on the monocyanoethylation of cyclohexanone. This reaction was conducted under various conditions, and yields of cyclohexanone-propionitrile (I) varied between 10 and 47%. Self-condensation of cyclohexanone can evidently also proceed under the action of strong alkaline agents under the conditions of cyanoethylation, with formation of cyclohexenylcyclohexanone (II) whose boiling point [4] is the same as that of nitrile (I). This precludes the separation of these compounds by simple rectification.

It was found that unsaturated ketone (II) can be identified in the mixture after hydrogen chloride has been passed into the latter. The structure of the resultant 1'-chlorocyclohexylcyclohexanone-2 (III) was confirmed by the preparation of the same substance by the action of hydrogen chloride on an authentic specimen of the ketone (II). Treatment of ketone (III) with hydrazine hydrate gave the previously described [5] 3,4-tetramethylene-5,5-pentamethylenepyrazoline (IV), which confirmed the position of the chlorine in ketone (III). Passage of hydrogen chloride into nitrile (I) evidently transformed it into a cyclic iminoether, since after treatment of the reaction mass with water we isolated 5,6-tetramethylenedihydropyrone-2 (V), previously described by R. Ya. Levina, N. P. Shusherina and M. Yu. Lurye [6].



We applied this reaction to the investigation of the influence of the conditions on the degree of purity of the nitrile (I) obtained. It was found that with sodium ethoxide the self-condensation of cyclohexanone even takes place at 7-8°. In this case nitrile (I) contained about 3% unsaturated ketone (II). Distillation of the reaction mass in presence of traces of alcoholate or of sulfuric acid (which was used for neutralization of the alkaline agents) leads to a sharp increase in the amount of ketone (II), the content of which under these conditions rises to 35-40%. The crotonic condensation does not go when cyanoethylation is conducted with Rodionov catalyst (this was confirmed by a blank experiment – heating of cyclohexanone with this catalyst), but the formation of appreciable amounts of di- and tetracyanoethylated cyclohexanone was observed.

Consequently, when carrying out the cyanoethylation of ketones in presence of alcoholates or caustic alkalies, we must avoid unnecessary heating, thoroughly neutralize the alkali at the end of the reaction, and (not least) carefully wash out traces of acid before distillation of the reaction mass.

The literature does not contain any data for the reaction of acrylonitrile with butyrone. There is merely a report to the effect that its homolog – diethyl ketone – adds on three molecules of acrylonitrile [1]. We found the conditions in which butyrone adds on one molecule of acrylonitrile to give γ-butyrylacrylonitrile. Similarly we prepared γ-benzoylvaleronitrile from propiophenone. (Only the dicyanoethylation of propiophenone had previously been described [1].) We synthesized the corresponding acid amides by hydrolysis of the δ-ketonitriles.

EXPERIMENTAL

Cyanoethylation of cyclohexanone. To 524 g cyclohexanone in presence of sodium ethoxide (from 0.25 g sodium and 3 ml anhydrous alcohol) was added 56 g acrylonitrile in 1 hour while stirring and cooling. The reaction mass was stirred 30 minutes with cooling and 2 hours at room temperature, neutralized with dilute acetic acid and washed with water until neutral. The excess of cyclohexanone was distilled off in vacuum, and cyclohexanone-propionitrile (I) was isolated from the residue by two distillations; yield 57 g (35.5%).

B.p. 122-123° (5 mm), n_D^{20} 1.4790. Literature data [3]: b.p. 125° (5 mm), n_D^{20} 1.4745.

Passage of dry hydrogen chloride through 15 g of the prepared nitrile (I) in absolute either yielded 0.5 g 1-chlorocyclohexylcyclohexanone-2 (III) with m.p. 41-43°. Literature data [7]: m.p. 41-43°. This yield is equivalent to about 3% of unsaturated ketone in the original nitrile (I). After separation of the crystals and washing with water, 5,6-tetramethylenedihydropyrone-2 (V) was isolated from the residue; yield 7.6 g.

B.p. 117-118° (8 mm), n_D^{20} 1.5057. Literature data [6]: b.p. 117-118° (5 mm), n_D^{20} 1.5050.

The content of ketone (II) in nitrile (I) rose to 38% when cyanoethylation was performed at a higher temperature (11-15°), neutralization was effected with dilute sulfuric acid and the excess of cyclohexanone was distilled off at atmospheric pressure.

490 g cyclohexanone was reacted with 53 g acrylonitrile in presence of 13 ml Rodionov catalyst (30 minutes at 60° and then 1 hour at 40°) and the mixture was then neutralized with 2 N hydrochloric acid and washed with water after removal of the cyclohexanone in vacuum. Yield 13 g (16%) of 2,2,6,6-tetracyanoethylcyclohexanone, m.p. 164° (from acetone [3]). From the residual oil, after vacuum distillation, was obtained 34 g (25%) of nitrile (I) with b.p. 128-130° (7-8 mm) and 33 g (35%) 2,2-dicyanoethylcyclohexanone with b.p. 241-242° (10 mm), m.p. 68° (from benzene)[3].

1-Cyclohexenylcyclohexanone-2 (II) was obtained by condensation of cyclohexanone by Mlesiva's method [4]. Yield 35%.

B.p. 143° (17 mm), n_D^{20} 1.5048, d_4^{20} 1.0029, MR_D 52.76; Calc. 52.76. Literature data [8]: b.p. 143-145° (16 mm), n_D^{20} 1.5049, d_4^{20} 1.001.

1'-Chlorocyclohexylcyclohexanone-2 (III). 15 g ketone (II) was saturated while cooling with dry hydrogen chloride until the reaction mass had solidified completely. The crystals were washed with water and recrystallized from anhydrous alcohol. Yield 12 g (66%) of compound with m.p. 41°. Literature data [7]: m.p. 41-43°. It does not give a depression of melting point in admixture with chloroketone (III) prepared in the synthesis of nitrile (I).

A solution of 9 g chloroketone (III) in 25 ml anhydrous alcohol was added to 5 g hydrazine hydrate. The mixture was boiled 2 hours. The pyrazoline (IV) was salted out with solid caustic alkali and distilled. Yield 3 g (37%).

B.p. 149-150° (10 mm), m.p. 61°. Literature data [5]: b.p. 164-166° (15 mm), m.p. 62°.

γ-Butyrylcapronitrile. To 200 g butyrone was added sodium ethoxide (from 0.4 g sodium in 10 ml alcohol) and, with continuous stirring, dropwise addition was made in the course of $2^1/_2$ hours of 46 g acrylonitrile. The mixture, which turned yellow, was then heated on a water bath at 50-60° for another 3 hours (without stopping the stirrer), left overnight, carefully neutralized with 2 N sulfuric acid (the minute precipitate formed during the reaction disappeared at this stage and the mixture became colorless) and washed 4-5 times with water. After drying with sodium sulfate, the reaction mass was distilled in vacuum. The original butyrone first came over (b.p. 50-60° at 20 mm), followed by 44 g (31%) γ-butyrylcapronitrile (VI), b.p. 130-140° (10 mm). After redistillation:

B.p. 101.5-102° (4 mm), n_D^{20} 1.4455, d_4^{20} 0.9255, MR_D 48.13; Calc. 48.22.

Found %: N 8.29, 8.36. $C_{10}H_{17}ON$. Calculated %: N 8.33.

The residue in the distillation flask was about 30 g of viscous liquid with b.p. 160 to 220° at 1 mm. Fractional distillation in vacuum yielded 6.4 g of a fraction corresponding to γ-ethyl-γ-butyrylpimelonitrile.

B.p. 209-210° (1 mm), n_D^{20} 1.4779, d_4^{20} 1.0013, MR_D 58.88; Calc. 59.46.

γ-Butyrylcaproic acid. A mixture of 5 g nitrile and 50 ml concentrated hydrochloric acid was refluxed for 30 hours. After cooling, excess caustic alkali was added and extraction was effected with ether; the aqueous layer was then again acidified with hydrochloric acid and extracted with ether. The ether layer was washed with water and dried with sodium sulfate; the ether was driven off and the residue distilled in a nitrogen stream to give 3.7 g (66%) acid, b.p. 164-165° (7 mm), n_D^{20} 1.4486, d_4^{20} 1.0125; MR_D 49.83; Calc. 49.92.

Found %: C 64.27, 64.36; H 9.81. 9.93. $C_{10}H_{18}O_3$. Calculated %: C 64.48; H 9.74.

γ-Benzoylvaleronitrile. Prepared in a similar manner to γ-benzoylcapronitrile [9] by the action of 10.6 g acrylonitrile on 62.7 g propiophenone. Yield of γ-benzoylvaleronitrile 27 g (72%).

B.p. 121-123° (17 mm), n_D^{20} 1.5261, d_4^{20} 1.0582, MR_D 54.25; Calc. 53.84.

Found %: C 76.95, 76.97; H 7.10, 7.27. $C_{12}H_{13}ON$. Calculated %: C 76.93; H 7.04.

Acidic hydrolysis of 10 g of this nitrile (as described above) gave 8 g (73%) of γ-benzoylvaleric acid.

B.p. 193° (2 mm), n_D^{20} 1.5310, d_4^{20} 1.1320, MR_D 56.37; Calc. 56.56.

Found %: C 69.79, 69.84; H 6.89. 6.91. $C_{12}H_{14}O_3$. Calculated %: C 69.88; H 6.83.

δ-Ketocapramide. A mixture of 10 g δ-ketocapronitrile [10], 250 ml of 3% solution of hydrogen peroxide, 100 ml ethanol and 2.5 ml of 6 N sodium hydroxide was heated 4 hours to 50-60° (with stirring). The cooled mixture was neutralized and evaporated on a water bath. The residue (a yellowish oil) crystallized after standing in a vacuum desiccator for several days. Recrystallization from benzene gave 8.0 g (69%) δ-ketocapramide with m.p. 113°. Literature data [11]: m.p. 114°.

γ,γ,γ',γ'-Tetramethyl-δ-ketoazeladiamide (m.p. 143° from anhydrous alcohol) was similarly prepared from 2.0 g γ,γ,γ',γ'-tetramethyl-δ-ketoazeladinitrile (b.p. 169-170° at 7 mm; prepared in 30% yield from acrylonitrile and diisopropyl ketone [12]). The yield of amide was 2.1 g (89%).

Found %: N 10.85, 11.02. $C_{13}H_{24}O_3N_2$. Calculated %: N 10.93.

γ,γ-Dimethyl-γ',γ'-pentamethylene-δ-ketoazeladinitrile was obtained by the action of acrylonitrile on cyclohexylisopropyl ketone. Yield 22%, m.p. 63° (from alcohol).

Found %: C 73.85, 73.99; H 9.36, 9.45. $C_{16}H_{24}ON_2$. Calculated %: C 73.80; H 9.29.

The corresponding diamide could not be isolated when an attempt was made to hydrolyze this dinitrile with alkaline hydrogen peroxide.

SUMMARY

A secondary process during the cyanoethylation of cyclohexanone is the formation of cyclohexenylcyclohexanone. The synthesis of some δ-ketoacids and their derivatives is described.

LITERATURE CITED

[1] H. Bruson and T. Riener, J. Am. Chem. Sec. 64, 2850 (1942).

[2] R. Ya. Levina, N. P. Shusherina and T. A. Kaminskaya, Proc. Acad. Sci. USSR, 86, 79 (1952); H. Baumgarten and R. Eifert, J. Am. Chem. Soc. 75, 3015 (1953).

[3] A. P. Terentyev and S. M. Gurvich, J. Gen. Chem. Supp. Vol. I, 404 (1953).

[4] J. Mlesiva, Chem. listy, 47, 1031 (1953).

[5] A. N. Kost and I. I. Grandberg, J. Gen. Chem. 25, 1719 (1955). (T.p. 1673).*

[6] R. Ya. Levina, N. P. Shusherina and M. Yu. Lurye, J. Gen. Chem. 26, 750 (1956). (T.p. 861).*

[7] O. Wallach, Ber. 46, 70 (1907).

[8] W. Carothers and D. Coffman, J. Am. Chem Soc. 54, 4974 (1932).

[9] A. N. Kost and A.P. Terentyev, J. Gen. Chem. 26, 1992 (1956). (T.p. 2219).*

[10] A. N. Kost, T. A. Shchegoleva and A. G. Yudin, J. Gen. Chem. 25, 2464 (1955). (T.p. 2351).*

[11] D. Vorlander and A. Knotzsch, Ann. 294, 317 (1896).

[12] L. Berkley and R. Levine, J. Am. Chem. Soc. 72, 3699 (1950).

Received November 9, 1955

Moscow State University

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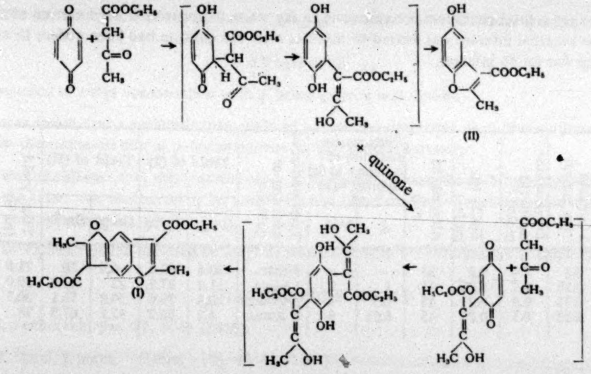
* T.p. = C. B. Translation pagination.

INVESTIGATIONS ON QUINONES

XII. THE REACTION OF p-BENZOQUINONE WITH ETHYL ACETOACETATE

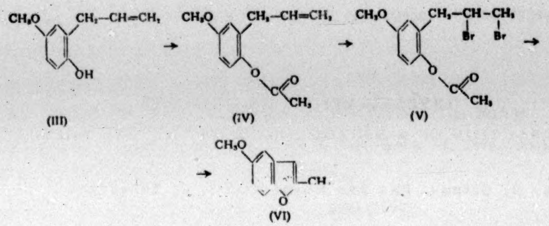
A. N. Grinev, Pan Bon Khvar and A. P. Terentyev

Condensation of p-benzoquinone with ethyl acetoacetate was effected by Pechmann [1] and leads to formation of two crystalline compounds belonging to the benzofuran and benzodifuran classes [2]. The structure of the substituted benzodifuran was proved by the investigations of Ikuta [2]. Graebe claimed that this compound was formed in rather better yield by treating quinone with excess of ethyl acetoacetate [3]. However, our own investigations, partly published [4], showed that a predominant yield of the benzodifuran derivative or of the benzofuran derivative depends mainly on the concentration in the reaction mixture of the p-benzoquinone which oxidizes the intermediate hydroquinone. Contrary to the view of Graebe [3], it is suggested that the main product even with a large excess of ethyl acetoacetate is the benzofuran derivative. But with increasing concentration of quinone in the reaction liquid the yield of diethyl ester of 2,6-dimethylbenzo-(1,2-b; 4,5-b')-difurana-3,7-dicarboxylic acid (I) increases.



Benzoquinone reacts with ethyl acetoacetate with formation of a carbon-carbon bond. This is proved by the formation of 2-methyl-3-carbethoxy-5-hydroxybenzofuran (II) with m.p. 137°, and not 2-methyl-3-carbethoxy-6-hydroxybenzofuran.

The structure of (II) was confirmed by its transformation into 2-methyl-5-methoxybenzofuran (VI). We also synthesized the latter by the classical method proposed by Claisen [5] for the preparation of 2-methylbenzofuran.



EXPERIMENTAL

1. Condensation of p-benzoquinone with ethyl acetoacetate. 35 g (0.25 mole) zinc chloride was dissolved in 45 ml anhydrous alcohol by heating in a flask fitted with a mechanical stirrer and a reflux condenser. To the solution was added 65 g (0.5 mole) ethyl acetoacetate, followed while heating (80-85°) and stirring by 27 g (0.25 mole) quinone in portions at the rate of approximately 1 g every 2 minutes. When the whole of the quinone had been added (about 1 hour after the start of the reaction), the mass was stirred and heated for 30 minutes at 80-85°. The reaction liquid solidified on cooling. The crystals were collected and dissolved in 250 ml ether. The insoluble residue was pure (I). Yield 11.2 g, m.p. 184°. The ether was driven off from the ethereal extract to give 21 g of (II) with m.p. 137° (from alcohol). Alcohol, zinc chloride, hydroquinone and ethyl acetoacetate were removed from the mother liquor by washing with water. A further 2 g of (II) was obtained. Total yield of (II) 23 g.

Results and experimental conditions are presented in the table. Experiments were carried out at 80-85°. In experiment 1 the reaction mixture was heated 45 minutes after the quinone had been added; in all the other experiments heating was for 30 minutes.

Experiment 1number	1 Quinone (in moles)	Ethyl aceto-acete (in mole)	$ZnCl_2$ (in moles)	Alcohol (in ml)	Portionwise addition of quinone at the approx. rate of		Total period of addition of quinone	Yield of (I)		Yield of (II)		Total yield (in %)
					g	min.		(in g)	(in %)	(in g)	(in %)	
1	0.2	0.4	0.2	35	—	—	5 min.	20.4	61.8	4.5	10	71.8
2	0.25	0.5	0.25	45	1	2	1 hour	11.2	27.2	23	41.8	69.0
3	0.25	0.5	0.25	45	0.5	4	3.5 hours	10.3	25.0	30.3	55.1	80.1
4	0.25	0.5	0.25	45	0.25	5	9 hours	4.2	10.2	37.3	67.8	78

2. 2-Methyl-3-carboxy-5-hydroxybenzofuran was obtained by hydrolysis of (II) with alcholic alkali. The experiment was carried out with 15.7 g (II), 9.6 g sodium hydroxide and 150 ml alcohol. The hydroxy acid was recrystallized from 50% acetic acid. Yield 13.5 g with m.p. above 360° (with decomp.).

3. 2-Methyl-3-carboxy-5-methoxybenzofuran. 13.5 g hydroxy acid was dissolved in alkali (5.7 g sodium hydroxide in 66 ml water). To the solution was gradually added 7 ml dimethyl sulfate with vigorous shaking, followed during methylation by another 7 ml dimethyl sulfate and 10 ml dioxane. The mixture was boiled 30 minutes. The liquid formed layers. 11.2 g sodium hydroxide was added and boiling continued until the liquid was homogeneous. The acid was separated by acidification with concentrated hydrochloric acid. Yield 14 g with m.p. 212° (from 50% acetic acid) in agreement with the literature [6].

4. 2-Methyl-5-methoxybenzofuran (VI). 14 g methoxy acid, pulverized and well mixed with 10 g calcium hydroxide, was heated in a Wurtz flask over a bare flame for about $1^1/_2$ hours. The oily liquid that came over was extracted with ether; the ether extract was dried with calcium chloride and the ether was driven off; the residue was then distilled at reduced pressure to give 6 g (54.5%) of (VI).

B.p. 117-118° for 10 mm, n_D^{20} 1.5674, d_4^{20} 1.1479, MR_D 46.18; Calc. 45.40.

Found %: C 74.27, 74.33; H 6.30, 6.35. $C_{10}H_{10}O_2$. Calculated %: C 74.04; H 6.21.

5. 2-Allyl-4-methoxyacetylphenol (IV). Obtained by acetylation of the known [7] 2-allyl-4-methoxyphenol (III) with acetic anhydride by the Claisen method [5]. 34 g of (III) was mixed with 43 ml acetic anhydride and 2 drops concentrated sulfuric acid was added. The mixture was heated on a water bath. The resultant oil was dissolved in ether, washed with water, then with dilute caustic alkali, and dried with magnesium sulfate. Distillation at reduced pressure gave 32 g of (IV).

B.p. 140-142° for 10 mm, n_D^{20} 1.5178.

Found %: C 69.31, 69.28; H 6.91, 7.11. $C_{12}H_{14}O_3$. Calculated %: C 69.88; H 6.84.

6. 2-Methyl-5-methoxybenzofuran (VI). To a solution of 31 g (IV) in 45 ml chloroform was gradually added 24 g bromine in 60 ml chloroform while cooling and stirring. As soon as the reaction was at an end, the chloroform was distilled off in vacuum. The colorless bromide (V) was mixed with a saturated solution of 43 g potassium hydroxide in methyl alcohol with cooling. The mixture was boiled 30 hours, the alcohol was taken off and the oil was extracted with ether. The ethereal solution was dried with calcium chloride and (VI) was distilled off at reduced pressure. Yield 11 g.

B.p. 118-120° for 10 mm, n_D^{20} 1.5669.

Found %: C 74.02, 74.13; H 6.55, 6.41. $C_{10}H_{10}O_2$. Calculated %: C 74.04; H 6.21.

SUMMARY

The reaction of ethyl acetoacetate with p-benzoquinone was studied.

1. It was shown that a predominating yield of benzofuran derivative or of benzodifuran derivative depends only on the concentration of p-benzoquinone in the reaction mixture.

2. It was established that this reaction leads to 2-methyl-3-carbethoxy-5-hydroxybenzofuran. The structure of the latter was confirmed by its transformation into 2-methyl-5-methoxybenzofuran which was also prepared by reverse synthesis.

3. A mechanism of the reaction of ethyl acetoacetate with p-benzoquinone is proposed.

LITERATURE CITED

[1] H. Pechmann, Ber. 21, 3005 (1888).

[2] M. Ikuta, J. prakt. Chem. [2], 45, 65 (1892).

[3] G. Graebe and S. Levy, Ann. 283, 245 (1894).

[4] A. P. Terentyev, A. N. Grinev and Pan Bon Khvar, J. Gen. Chem 24, 2050 (1954). (T.p. 2015)[*]

[5] L. Claisen, Ann.418, 69 (1910).

[6] E. Bernatek, Acta Chem.Scand. 7, 677 (1953).

[7] F. Mauthner, J. prakt. Chem [2], 102, 41 (1921).

Received October 10, 1955

Moscow State University

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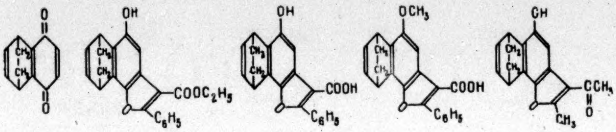
[*] T.p. = C. B. Translation pagination.

INVESTIGATIONS ON QUINONES

XIII. PREPARATION OF ENDOETHYLENENAPHTHOFURANS

A. N. Grinev, A. B. Terentyev and A. P. Terentyev

Several reactions of 5,8-endoethylene-1,4-naphthoquinone (I) were described in one of our recent papers [1]. This quinone differs from other quinones of the dihydronaphthalene series in being stable towards various reagents. Its properties are reminiscent of those of ordinary p-quinones. In the present work we succeed in performing the reactions of (I) with benzoylacetic ester and acetylacetone. The following were prepared: the ethyl ester of 2-phenyl-6,9-endoethylene-5-hydroxynaphthofuran-3-carboxylic acid (II), 2-phenyl-6,9-endoethylene-5-hydroxynaphthofuran-3-carboxylic acid (III), 2-phenyl-6,9-endoethylene-5-methoxynaphthofuran-3-carboxylic acid (IV) and 2-methyl-6,9-endoethylene-5-hydroxy-3-acetylnaphthofuran (V):



EXPERIMENTAL

1. Ethyl ester of 2-phenyl-6,9-endoethylene-5-hydroxynaphthofuran-3-carboxylic acid (II). To a solution of 5 g zinc chloride in 6.5 ml anhydrous ethyl alcohol and 10 ml benzoylacetic ester was added 7 g of (I), in portions, in the course of 3-5 minutes with heating on the water bath and stirring; the mass was then heated for another 40 minutes at 80-90°. Yield 8.3 g (63%) of (II), m.p. 200-201° (from acetic acid).

Found %: C 76.81, 76.62; H 5.83, 5.86. $C_{23}H_{20}O_4$. Calculated %: C 76.60; H 5.58.

2. 2-Phenyl-6,9-endoethylene-5-hydroxynaphthofuran-3-carboxylic acid (III). Acid III was obtained by hydrolysis of (II) with alcoholic alkali. The experiment was carried out with 5 g of ester (II), 40 ml alcohol and 3.5 g sodium hydroxide. Yield 4.5 g (III), m.p. 221-222°(from aqueous alcohol).

Found %: C 75.95, 75.87; H 5.54, 5.60. $C_{21}H_{16}O_4$. Calculated %: C 75.90; H 4.85.

3. 2-Phenyl-6,9-endoethylene-5-methoxynapthofuran-3-carboxylic acid (IV). (III) was methylated in the usual manner. The experiment was carried out with 3 g (III), 15 ml 2 N sodium hydroxide and 2 ml dimethyl sulfate. The excess of dimethyl sulfate was decomposed by heating with aqueous alkali. Yield 2.5 g (IV) with m.p. 201-202° (from acetic acid).

Found %: C 75.90, 76.02; H 5.45, 5.36. $C_{22}H_{18}O_4$. Calculated %: C 76.27; H 5.23.

4. 2-Methyl-6,9-endoethylene-5-hydroxy-3-acetylnaphthofuran (V). The reaction was carried out under the conditions of experiment 1, using 7 g (I), 14 ml acetylacetone, 6 g zinc chloride and 8 ml anhydrous alcohol. Yield 6.2 g (V) (58%). m.p. 274-275° (from alcohol).

Found %: C 76.36, 76.20; H 6.31, 6.20. $C_{17}H_{12}O_3$. Calculated %: C 76.10; H 6.01.

SUMMARY

Some substituted endoethylenenaphthofurans were prepared by condensation of 5,8-endoethylenenaphthoquinone with benzoylacetic ester and with acetylacetone.

LITERATURE CITED

[1] A. N. Grinev, A. B. Terentyev and A. P. Terentyev, J. Gen. Chem. 26, 730 (1956). (T.p. 837)*

Received October 10, 1955 Moscow State University

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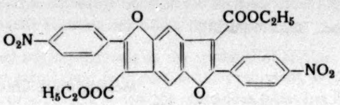
* T.p. = C. B. Translation pagination.

INVESTIGATIONS ON QUINONES

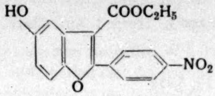
XIV. THE REACTION OF p-BENZOQUINONE WITH p-NITRO- AND p-BROMOBENZOYLACETIC ESTERS

A. N. Grinev, N. K. Venevtseva and A. P. Terentyev

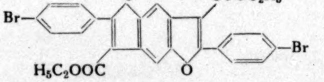
Like benzoylacetic ester, whose reaction with p-quinones we have already studied in some detail [1-4], p-nitro- and p-bromobenzoylacetic esters* enter into reaction with p-benzoquinone. The yield of substituted benzofurans and benzodifurans, however, is considerably lower than in the case of benzoylacetic ester, and resins are formed that hinder the isolation of the basic product. The following were prepared: diethyl ester of 2,6-di-p-nitrophenylbenzo-(1,2-b; 4,5-b')-difuran-3, 7-dicarboxylic acid (I), the ethyl ester of 2-p-nitrophenyl-5-benzofuran-3-carboxylic acid (II), the diethyl ester of 2,6-di-p-bromophenylbenzo-(1,2-b; 4,5-b')-difuran-3, 7-dicarboxylic acid (III) and the diethyl ester of 2-p-bromophenyl-5-benzofuran-3-carboxylic acid (IV):

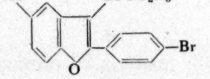


(I)



(II)





EXPERIMENTAL

Condensation of p-nitrobenzoylacetic ester with p-benzoquinone. To a solution of zinc chloride (3.5 g) in anhydrous alcohol (4 ml) was added 6.2 g p-nitrobenzoylacetic ester. The solution obtained by heating to 80-85° was mixed with 2.8 g p-benzoquinone and heated at 80-85° for 40 minutes. Crystals began to deposit from the reaction solution only 5-10 minutes after the start of the reaction. The crystals were filtered, washed with ether and then extracted with alcohol in an extractor. From the alcoholic solution was obtained 2.3 g of bright-yellow crystals of (II). M.p. 208-210° (from alcohol).

Found %: C 62.47, 62.66; H 4.36, 4.37. $C_{17}H_{13}O_6N$. Calculated %: C 62.38; H 4.005.

The alcohol-insoluble yellow, crystalline residue was recrystallized from nitrobenzene to give 0.9 g of yellow crystals of (I) with m.p. 348-350°.

Found %: C 61.84, 61.96; H 3.83, 3.91. $C_{28}H_{20}O_{10}N_2$. Calculated %: C 61.76; H 3.70.

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* Substituted benzoylacetic esters are obtained by hydrolysis of p-nitro- and p-bromobenzoylacetoacetic esters [5, 6].

2. Condensation of p-bromobenzoylacetic ester with p-benzoquinone. The reaction was performed under conditions similar to those of the preceding experiment, using 7 g zinc chloride, 8 ml anhydrous alcohol, 13.15 g p-bromobenzoylacetic ester and 5.5 g p-benzoquinone. The crystals formed in the course of the reaction were separated, washed with ether and recrystallized from dioxane to give 0.77 g white crystals of (III). M.p. 300-302°.

Found %: C 55.30, 55.25; H 3.53, 3.56. $C_{28}H_{20}O_6Br_2$. Calculated %: C 54.92; H 3.29.

The ethereal solution was dried over calcium chloride and the ether evaporated. The crystals formed were washed in benzene and recrystallized from dichloroethane. Yield 2.9 g (IV). M. p. 170-171°.

Found %: C 56.29, 56.27; H 3.64, 3.55. $C_{17}H_{13}O_4Br$. Calculated %: C 56.50; H 3.62.

SUMMARY

Condensation of p-benzoquinone with p-nitro- and p-bromobenzoylacetic esters leads to formation of derivatives of benzofuran and benzodifuran.

LITERATURE CITED

[1] A. N. Grinev, V. N. Frosin and A. P. Terentyev, J. Gen. Chem, 25, 523 (1955). (T.p. 491)*

[2] A. N. Grinev, Pan Bon Khvar, V. N. Frosin and A. P. Terentyev, J. Gen. Chem 26, 561 (1956). (T.p. 528).*

[3] A. N. Grinev, A. B. Terentyev and A. P. Terentyev, J. Gen. Chem. 26, 730 (1956). (T.p. 837).*

[4] A. N. Grinev, Pan Bon Khvar and A. P. Terentyev, Herald of Moscow State Univ. 2, 91 (1956).

[5] Bulow and E. Hailer, Ber. 35, 931 (1902).

[6] W. Hall and L. Thorp, J. Am. Chem. Soc. 35, 270 (1913).

Received October 10, 1955

Moscow State University

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* T. p. = C. B. Translation pagination.

THE SYNTHESIS OF HOMOLOGS OF TAURINE BY THE LEUCKART REACTION

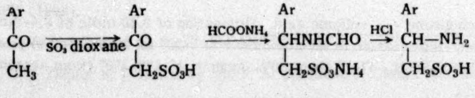
A. P. Terentyev, V. M. Potapov and I. Z. Semion

Compounds of the taurine series, i.e., various β-aminosulfonic acids of the structure $RCHNH_2CH_2SO_3H$, have recently been attracting ever increasing attention. A number of taurine derivatives have been proposed as surface-active agents for the textile and paper industries [1]. Data have been published for the antibacterial activity of taurine derivatives [2]. Compounds of the taurine series have also been tested as components of sulfamide preparations [3].

Several methods have been proposed for the preparation of taurine derivatives, starting from hydroxysulfonic acids [4], aminoalcohols [5], halosulfonic acids [6], dihalo compounds [7], and unsaturated sulfonic acids [8]. Taurine and its homologs are formed by oxidative cleavage of thiazole compounds [9] and cystine [10]. Preparation of taurines from nitroketones [11], nitrosulfonic acids [12] and aldehydosulfonic acids [13] has also been proposed.

In spite of the apparent diversity of possibilities, a convenient preparative method has not hitherto been available for taurine homologs because the methods cited above either require difficultly accessible starting substances or drastic reaction conditions (high pressures).

We carried out experiments on the synthesis of taurines by reductive amination of β-ketosulfonic acids by the action of ammonium formate (Leuckart reaction), in the anticipation that the starting β-ketosulfonic acids would become readily accessible substances, following investigations in our laboratory [14] and somewhat later by Truce and Alfieri [15] in Suter's laboratory.



$$\begin{array}{l}Ar\\ |\\ CO\\ |\\ CH_3\end{array} \xrightarrow{SO_3\text{, dioxane}} \begin{array}{l}Ar\\ |\\ CO\\ |\\ CH_2SO_3H\end{array} \xrightarrow{HCOONH_4} \begin{array}{l}Ar\\ |\\ CHNHCHO\\ |\\ CH_2SO_3NH_4\end{array} \xrightarrow{HCl} \begin{array}{l}Ar\\ |\\ CH{-}NH_2\\ |\\ CH_2SO_3H\end{array}$$

Starting substances were acetophenone and its homologs – 4-methylacetophenone and 2,4-dimethylacetophenone. After converting these ketones into the corresponding ω-sulfonic acids by the action of dioxane-sulfotrioxide, we introduced the latter (as the ammonium or barium salts) into the Leuckart reaction and obtained the expected β-aminosulfonic acids which are aromatic homologs of taurine. Suitable reactants, as is usual for Leuckart reactions, are ammonium formate or formamide or a mixture of these obtained by the action of formic acid on ammonium carbonate. Good results are also obtained when using urea in admixture with anhydrous formic acid.

EXPERIMENTAL

β-Phenyltaurine, $C_6H_5CHNH_2CH_2SO_3H$. Acetophenonesulfonic acid, prepared from 0.4 mole acetophenone and dioxane-sulfotrioxide [15], was neutralized with aqueous ammonia and the solution was evaporated to dryness. The unpurified ammonium salt was mixed with 1 mole formamide and heated at 165° (thermometer in liquid) in a flask with a sloping condenser for 6 hours. After cooling, 60 ml alcohol was added to the reaction mass and the precipitate of ammonium salt of N-formyl-β-phenyltaurine was filtered off and recrystallized from water. Yield 62.4 % calculated on the original acetophenone, decomp. p. 231°. The preparation is not analytically pure (analysis gives a slightly too high carbon content). Addition of 7 ml conc. H_2SO_4 to 0.03 mole of ammonium salt dissolved in 25 ml boiling water quickly brought down β-phenyltaurine which was purified by dissolving in aqueous ammonia and reprecipitating with hydrochloric or sulfuric acid.

β-Phenyltaurine forms characteristic hexagonal plates, insoluble in organic solvents, poorly soluble in hot water and nearly insoluble in cold water; the compound dissolves in caustic alkalies. Decomp. p. 314° (in block).

Found %: C 47.55; H 5.32; N 7 11; S 16.17. $C_8H_{11}O_3NS$. Calculated %: C 47.76; H 5.51; N 6.96; S 15.92.

Determination of nitrogen by the Van Slyke method (micromethod) showed that the whole of the nitrogen is in the primary amino group.

For final proof of the structure, the prepared β-phenyltaurine was converted into the amide of styrene-β-sulfonic acid by the action of sodium nitrite followed by the action of phosphorus pentachloride and ammonia. A mixed specimen with the compound obtained by sulfonation of styrene followed by treatment with PCl_5 and NH_3 did not give a depression of melting point.

The barium salt of acetophenonesulfonic acid can be used in place of the ammonium salt in the preparation of β-phenyltaurine, while formamide can be replaced by ammonium formate (5 hours with gradual rise of temperature to 200°). The optimum yield (64 % calculated on the original ketone) is obtained with a molar ratio of ketone-sulfonic acid to formate of 1:2; A large excess of formate leads to lower yields. Hydrogen sulfide comes off during the reaction (detected by odor), indicating partial destruction of the sulfo group during the Leuckart reaction and explaining the low yields.

β-(p-Tolyl)-taurine, $p\text{-}CH_3C_6H_4CHNH_2CH_2SO_3H$. The ammonium salt of the sulfonic acid, prepared similarly to the above from 0.125 mole p-methylacetophenone, was heated with 0.4 mole ammonium formate for 2 hours with gradual rise of temperature to 220°; the product was worked up as described above. Yield 29 % calculated on the original ketone. The properties of β-(p-tolyl)-taurine are entirely similar to those of β-phenyltaurine.

Decomp. p. approx. 347°.

Found %: C 50.50; H 6.15; N 6.74. $C_9H_{13}O_3NS$. Calculated %: C 50.23; H 6.09; N 6.51.

2,4-Dimethylacetopheneone -ω- sulfonic acid. Sulfonation of 0.40 mole of 2,4-dimethylacetophenone with a suspension of dioxane-sulfotrioxide in dichloroethane at 5-15° for 2 hours led to precipitation of the free sulfonic acid $(CH_3)_2C_6H_3COCH_2SO_3H$. Yield about 80%, decomp. p. 178-179° (from acetone).

Found %: C 50.80; H 5.71. Equivalent (titration against methyl orange) 232. $C_{10}H_{12}O_4S \cdot \frac{1}{2} H_2O$. Calculated %: C 50.70; H 5.49. M 237.1.

The ammonium salt decomposes at 170-171° (from water followed by washing with methanol and ether). The S-benzylthiuronium salt has m.p. 156° (from water).

β-(m-Xylyl)-taurine $(CH_3)_2C_6H_3CHNH_2CH_2SO_3H$. A mixture of 0.05 mole of ammonium salt of 2,4-dimethylacetophenone-ω-sulfonic acid with 6 g urea and 15 ml anhydrous formic acid was refluxed for 6 hours (the temperature was gradually raised from 120 to 150°), after which the mixture was boiled 30 minutes with 40 ml hydrochloric acid (1:1). The resultant precipitate of β-(m-xylyl)-taurine was purified via the ammonium salt. M.p. 312°. Yield of pure compound 47 %.

Found %: C 52.64; H 6.79; N 6.36. $C_{10}H_{15}O_3NS$. Calculated %: C 52.39; H 6.60; N 6.11.

SUMMARY

1. The Leuckart reaction was extended to a new class of compounds – β-ketosulfonic acids.

2. β-Phenyltaurine and its 4-methyl- and 2,4-dimethyl- homologs were obtained from the corresponding β-ketosulfonic acids by Leuckart reductive amination.

LITERATURE CITED

[1] R. A. Duncan, Ind. Eng. Chem. 26, 25 (1934); E. D. Lederer, Angew. Chem. 47, 119 (1934); British Pat. 461614 (1937); C. A. 31, 5480 (1937); British pat. 473760 (1937); C. A. 32, 3055 (1938); U.S. Pat. 2213184 (1940); C. A. 35, 829 (1941).

[2] R. Kuhn, T. Wieland and E. F. Moller, Ber. 74, 1605 (1941); M. McIlwain, Brit. J. Exptl. Path. 23, 95 (1942); C. A., 36, 6186 (1942); E. E. Snell, J. Biol. Chem. 139, 975 (1941); M. M. Rapport, J. F. Mead, J. T. Maynard, A. E. Senear and J. B. Koepfli, J. Am. Chem. Soc. 69, 2561 (1947); V. H. Cheldelin and C. A. Schink, J. Am. Chem. Soc. 69, 2625 (1947); G. Svanovics, Magyar Biol. Kutatointeret. Munkai 15, 462 (1943); C. A. 42, 143 (1948); A. Gandini, Farmaco sci. e. tec. 1, 83 (1946); C. A. 40, 6417 (1946); J. T. Bernett, D. J. Dupre, B. J. Hollowey and F. A. Robinson, J. Chem. Soc. 1944, 94; R. Winterbottom, J. W. Clapp, W. H. Miller, J. P. English and R. O. Roblin, J. Am. Chem. Soc. 69, 1393 (1947).

[3] E. Miller, J. M. Spargeu, L. W. Kissinger, and L. F. McBurney, J. Am. Chem Soc. 62, 2099 (1940).

[4] A. Strecker, Ann. 91, 87 (1854); F. Carl, Ber. 12, 1604 (1879); U. S. Pat. 1932907 (1933); C. A. 28, 491 (1934); German pat. 589948 (1933); C. A. 28, 2370 (1934); H. Kolbe, Ann. 122, 33 (1862).

[5] U. S. Pat. 406380 (1934); C. A. 28, 4746 (1934); A. Reychler, Bull. Soc. Chim. Belg. 32, 247 (1923); F. Cortese, J. Am. Chem. Soc. 58, 191 (1936); S. Gabriel, Ber. 21, 2664 (1888).

[6] F. P. Kohler, Am. Chem. J. 20, 692 (1898).

[7] C. S. Marvel, C. F. Bailey and M. S. Sparberg, J. Am. Chem. Soc. 49, 1833 (1927); J. W. Schick and E. F. Degering, Ind. Eng. Chem. 29, 906 (1947).

[8] German Pat. 573304 (1931); C. A. 27, 2965 (1933); A. Lambert and J. D. Rose, J. Chem. Soc. 1949 46; German Pat. 612536 (1935); C. A. 29, 6251 (1935).

[9] S. Gabriel, Ber. 22, 1153, 2987 (1889); C. Avenarius, Ber. 24, 266 (1891); S. Gabriel and J. Colman, Ber. 39, 2889 (1906); C. Bookman, Ber. 28, 3116 (1895); S. Gabriel and W. E. Lauer, Ber. 23, 92 (1890); G. Pinkus, Ber. 26, 1079 (1893).

[10] German Pat. 604016 (1934); C. A. 29, 818 (1935).

[11] J. Bernett, D. J. Dupre, B. J. Hollowey and F. A. Robinson, J. Chem. Soc. 1944, 94.

[12] R. L. Heath and H. A. Piggott, J. Chem. Soc. 1947, 1481; J. M. H. Gold, L. J. Ducker, R. Yotter, C. J. B. Thor and G. Lang, J. Org. Chem 16, 1495 (1951); J. M. H. Gold, M. Skebelsky and G. Lang, J. Org. Chem. 16, 1500 (1951).

[13] J. A. A. Auries, Rev. gen. de chim. pure (Bordeaux). 14, 278 (1911); Chem. Zentr. 1911, II, 1433; French Pat. 801562 (1936); C. A., 31, 420 (1937); German Pat. 656417 (1938); C. A. 32, 2519 (1938).

[14] A. P. Terentyev and L. A. Yanovskaya, Proc. Acad. Sci. USSR 75, 235 (1950).

[15] W. E. Truce and C. C. Alfieri, J. Am. Chem. Soc. 72, 2740 (1950).

Received November 18, 1955

Moscow State University

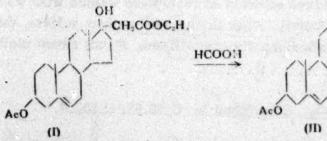
SOME PROPERTIES OF ESTERS OF p-TOLUENESULFONIC ACID WITH 17β-HYDROXYSTEROIDS

V. STUDY OF THE PRODUCTS OF DEHYDRATION OF 17α-METHYLANDROSTANEDIOL-3β,17 AND ITS DERIVATIVES

O. S. Madaeva

Cleavage of p-toluenesulfonic acid from the 3-acetate of the 17-tosylate of Δ^5-androstendiol-3β,17β gives, as was previously shown [1], a mixture of compounds with a positive color reaction in the Kagi and Miescher test [12] which is characteristic of retro-compounds of this series. From such a mixture was isolated only one individual 18-nor-derivative with m.p. 95-96° and containing a ditertiary double bond. It was of interest to prepare an 18-nor-compound of the androstane series with a secondary-tertiary double bond.

Magrath, Petrow et al. [3] showed that heating of the ethyl ester of the 3-acetate of Δ^5-pregnenediol-3β, 17α-carboxylic acid-21 (I) with anhydrous formic acid leads to dehydration accompanied by a structural change of the steroid skeleton. On the basis of the negative reaction with nitrosochloride in the Thiele test [4], the authors concluded that the double bond formed in compound (II) has a secondary-tertiary character and is between C_{12} and C_{13}.



We studied this reaction with reference to the dehydration of 17α-methylandrostanediol-3β,17 (IV).

Heating of 17α-methylandrostanediol-3β,17 (IV) with 98% formic acid gave compound (V) with m.p. 75.5-76.5°, $[\alpha]_D^{20}$ 41.7° (c = 1; chloroform). It gave a yellow color with tetranitromethane, a negative Thiele color reaction and a positive result in the Kagi-Miescher test; in elementary composition it corresponded to a product of dehydration of (IV). Hydrolysis of (V) with an aqueous alcoholic solution of potassium carbonate led to the corresponding carbinol (VI) with m.p. 132-133°. Hydrogenation of (VI) in glacial acetic acid in presence of reduced platinum oxide gave the saturated compound (VII) with m. p. 132-133°, corresponding in elementary composition to 17β-methylandrostanol-3β (XIV). However, a mixture of compound (VII) with compound (XIV) [5], which has the normal steroid skeleton, exhibited a melting point depression; the mixture started to melt at 125°.

Consequently (VII) is the isomer of (XIV) with an altered steroid carbon skeleton, thus demonstrating that dehydration of (IV) proceeded with retropinacoline rearrangement. In this case two isomers could be formed: (V) with secondary-tertiary double bond $C_{12, 13}$ and (Va) with ditertiary double bond $C_{13, 14}$.

For the purpose of conclusive proof of the position of the double bond, compound (V), obtained after dehydration of (IV), was subjected to hydroxylation with osmium oxide in ethereal solution. The triol (VIII) with diffuse m.p. 202-207° was isolated. It crystallized from acetone in two forms: needles and plates corresponding to the isomeric α,α- and β,β-diols. They could not be separated by crystallization. Acetylation of the triol with acetic anhydride in pyridine at room temperature gave the corresponding diacetate, one acetyl group of which was formed at the expense of the secondary hydroxyl at C_3; formation of a second acetyl group indicates that of the two hydroxyl groups resulting from hydroxylation of the double bond, one is secondary. Consequently, the secondary-tertiary nature of the double bond of (V) was established and in turn its location between C_{12} and C_{13}. The prepared 3,12-diacetate of 18-nor-17,17-dimethylandrostanetriol-3β,12β,13β (IX) has m.p. 184-184.5°.

In the course of this verification of the structure of (VII) we synthesized the acetate of 17-methylandrostanol-3β [5](XIV) by hydrogenation of a mixture of the acetate of $\Delta^{5,16}$-17-methylandrostadienol-3β (XI) and the acetate of 17-methylene-Δ^5-androstanol-3β (XII). The latter were obtained by reaction of the 3-acetate of 17α-methyl-Δ^5-androstenediol-3β,17 (X) with phosphorus oxychloride [6].

EXPERIMENTAL

17α-Methylandrostanediol-3β,17 (IV). 5 g of 17α-methyl-Δ^5-androstenediol-3β,17 (III) was dissolved in 220 ml glacial acetic acid distilled over potassium permanganate, and was hydrogenated with hydrogen in presence of platinum catalyst (0.6 g platinum oxide previously reduced in 60 ml glacial acetic acid). Hydrogenation was completed in 2 hours and the amount of hydrogen absorbed corresponded to 2 moles. The catalyst was filtered off, the acetic anhydride was distilled off in vacuum. Water was added to the residue and ether extraction was performed. The ether extract was washed with water, with 2% sodium bicarbonate solution and again with water; it was then dried with sodium sulfate. The ether was driven off to leave 5 g of substance with m.p. 204-207°; it recrystallized from 130 ml ethyl acetate in the form of needles. Yield 3.8 g with m.p. 210-211°. According to the literature the melting point of (V) prepared from androstanol-3β-one-17 is 210-211° [5] or 211-212° [7].

Formate of 17, 17-dimethyl-18-nor-Δ^{12}-androstenol-3β (V). 3.8 g of (IV) was dissolved in 19 ml 98% formic acid and heated at 90° for 5-7 minutes. The mixture was then cooled, poured into 30 ml water and extracted several times with ether. The combined ethereal extracts were washed with water, with sodium bicarbonate solution and again with water until neutral. After drying with sodium sulfate, the ether was distilled off. The residue (3.75 g) was an oily substance which rapidly crystallized. Prisms (from methanol) with m.p. 75-76.5°, $[\alpha]_D^{20}$ -41.7° (c = 1; chloroform).

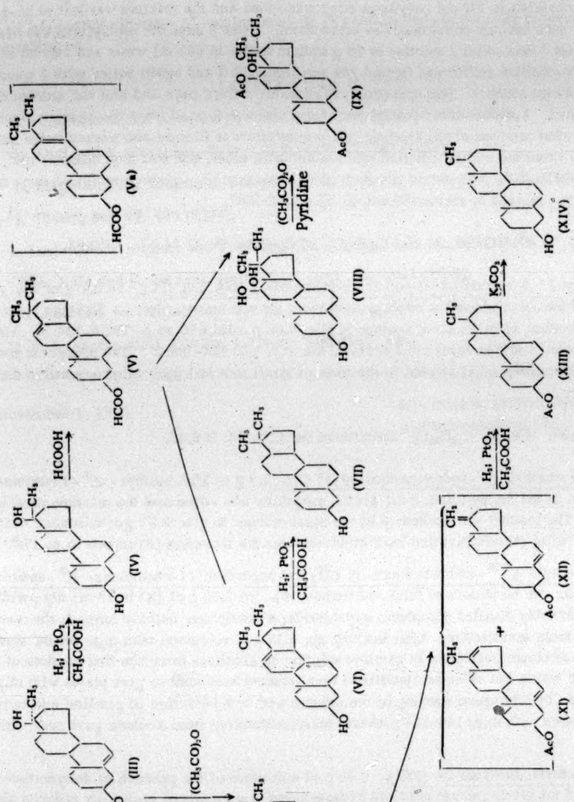
Found %: C 79.79; H 10.19. $C_{21}H_{32}O_2$. Calculated %: C 79.68; H 10.19.

17,17-Dimethyl-18-nor-Δ^{12}-androstenol-3β (VI). 0.35 g of (V) was dissolved in 5 ml methanol, an aqueous solution of potassium carbonate was added (0.23 g in 0.42 ml water) and the mixture boiled for 1 hour 15 minutes. A precipitate appeared on cooling and was filtered and washed with water until neutral and then dried in a vacuum-desiccator at 40°. Yield 0.25 g with m.p. 131-133°; after recrystallization from acetone the m.p. was 134-135°

Found %: C 83.42; H 11.31. $C_{20}H_{32}O$. Calculated %: C 83.25; H 11.18.

17,17-Dimethyl-18-nor-androstanol-3β (VII). 0.12 g (VI) was dissolved in 4 ml glacial acetic acid and exhaustively hydrogenated with hydrogen in presence of previously reduced platinum oxide (0.03 g in 4 ml glacial acetic acid); the calculated amount of hydrogen was absorbed (1 mole). After working up in the usual manner and distillation of the ether, 0.11 g of a white crystalline substance was obtained with m.p. 126-129°; several recrystallizations from aqueous methanol gave needles with m.p. 132-133°. $[\alpha]_D^{20}$ -14.66 (c = 1; chloroform).

Found %: C 82.58; H 11.78. $C_{20}H_{34}O$. Calculated %: 82.61; H 11.82.


(III)
$\frac{H_2; PtO_2}{CH_3COOH}$
(IV)
HCOOH
(V)
(Va)
(CH₃CO)₂O
(X)
(VI)
$\frac{H_2; PtO_2}{CH_3COOH}$
(VII)
(VIII)
(CH₃CO)₂O Pyridine
(IX)
(XI)
(XII)
$\frac{H_2; PtO_2}{CH_3COOH}$
(XIII)
K₂CO₃
(XIV)

A mixture with 17-methylandrostanol-3β (XIV), with m.p. 139.5-140°, gave a depression of melting point; the mixture started to melt at 125°.

17,17-Dimethyl-18-nor-androstanetriol-3β,12,13 (VIII). 3.11 g of (V) was dissolved in 78 ml anhydrous ether, 2.7 g osmium anhydride in 120 ml anhydrous ether was added and the mixture was left at 15-16°. A dark precipitate of osmium ester quickly commenced to come down. After 3 days the precipitate was filtered, washed with ether and boiled for 2 hours with a solution of 10 g sodium sulfite in 500 ml water and 280 ml ethyl alcohol; a precipitate of sodium-osmium sulfite was formed and was filtered off and again boiled with 5 g sodium sulfite in 250 ml water and 140 ml alcohol. This operation was repeated a third time and half the amount of sodium sulfite, water and alcohol. A dark-colored precipitate of the triol was formed from the aqueous alcoholic filtrates on standing and after removal of the alcohol; the precipitate was filtered and washed twice with a small quantity of water, with saturated sodium chloride solution and with ether, and was then dried at 100°. 1.74 g of the product was recrystallized from methanol and then from acetone to give plates containing some small needles; the needles could not be removed by recrystallization. M.p. 202-207°.

Found %: C 74.50, 74.67; H 10.83, 10.50. $C_{20}H_{34}O_3$. Calculated %: C 74.47; H 10.63.

3,12-Diacetate of 17, 17-dimethyl-18-nor-androstanetriol-3β,12β,13β (IX). To 0.1 g of triol (VIII), dissolved in 2 ml dry pyridine, was added 1 ml acetic anhydride; the mixture was left for 36 hours at room temperature. It was then worked up in the usual manner to give 0.09 g solid with m.p. 182.5-184.5°. After recrystallization from ethyl alcohol and then from ethyl acetate, the m.p. was 184-184.5°. The product is poorly soluble in ether. It crystallizes from ethyl alcohol in the form of small rods and from ethyl acetate in the form of hexagonal prisms.

Found %: C 70.94; H 9.49. $C_{24}H_{38}O_5$. Calculated %: C 70.88; H 9.42.

3-Acetate of 17α-methyl-Δ^5-androstenediol-3β,17 (X). 2.7 g of 17α-methyl-Δ^5-androstenediol-3β, 17 (III) was dissolved in 11 ml dry pyridine; 3 ml acetic anhydride was added and the mixture stood for 48 hours at room temperature. The product was worked up in the usual manner to give 2.97 g of substance with m.p. 168-172°, rising to 175-176° after recrystallization from ethyl acetate; the literature [8] reports m.p. 174°.

Acetate of 17-methyl-$\Delta^{5,12}$-androstadienol-3β (XI) and acetate of 17-methylene-Δ^5-androstenol-3β (XII) were obtained under the conditions of Julia and Heusser [6]. To 1.33 g of (X) in 12 ml dry pyridine at -12° was added in drops 1.8 ml freshly distilled phosphorus oxychloride; a precipitate quickly formed; the reaction mass was left for 17 hours at room temperature. After working up, 1.13 g of substance with m.p. 86-94° was obtained. 1.06 g of the substance was chromatographed in gasoline solution on alumina; from the first portions of eluate was obtained an oily residue which was twice recrystallized from aqueous methanol to give plates with m.p. 93-94°. From the eluate obtained by subsequent washing of the column with a 9:1 mixture of gasoline and benzene was isolated 0.58 g of substance with m.p. 114-134°; several recrystallizations from acetone gave rods with m.p. 133-134°.

Acetate of 17-methylandrostanol-3β (XIII). 0.48 g of a mixture of the products of dehydration of (XI) and (XII) was dissolved in 16 ml glacial acetic acid and hydrogenated in presence of previously reduced platinum oxide (0.8 g PtO_2 in 25 ml glacial acetic acid). The theoretical amount of hydrogen was absorbed in 30 minutes. After working up in the usual manner, an oil was obtained which crystallized on standing. Yield 0.25 g with m.p. 84-92°. Recrystallization from methanol gave needles with m.p. 94-95° in agreement with the literature [6]. $[\alpha]_D^{20}$ -8.18° (c = 1; chloroform).

17-Methylandrostanol-3β (XIV). 0.15 g of (XIII) was dissolved in 2.5 ml methanol and boiled with a solution of 0.2 g potassium carbonate in 1 ml water for 1 hour 15 minutes. Yield 0.13 g needles with m.p. 137-139.5°, rising to 139.5-140° [6] after recrystallization from alcohol.

Found %: C 82.89; 82.92; H 11.74, 11.92. $C_{20}H_{34}O$. Calculated %: C 82.68; H 11.80.

SUMMARY

1. Heating of the acetate of 17α-methylandrostanediol-3β,17 with 98% formic acid leads to dehydration with pinacoline rearrangement.

2. 17,17-Dimethyl-18-nor-Δ^5-androstenol-3β (V) and its derivatives were prepared and the structure of (V) was established.

LITERATURE CITED

[1] O. O. Madaeva and F. A. Luryi, Proc. Acad. Sci. USSR 84, 713 (1952).

[2] H. Kagi and K. Miescher, Helv. Chim. Acta 22, 683 (1939).

[3] D. Magrath, D. S. Morris, V. Petrow, and G. Royer, J. Chem. Soc. 1950, 2393.

[4] J. Thiele, Ber. 27, 454 (1894).

[5] L. Ruzichka, P. Meister and V. Prelog, Helv. Chim. Acta 30, 867 (1947).

[6] S. A. Julia and H. Heusser, Helv. Chim Acta, 35, 2080.(1952).

[7] L. Ruzicka, N. W. Golberg and H. R. Rosenberg, Helv. Chim. Acta 18, 1498 (1935).

[8] D. H. R. Barton and J. D. Cox, J. Chem. Soc. 1948, 890.

Received November 1, 1955

All-Union S. Ordzhonikidze Institute
of Pharmaceutical Chemical Research

JOURNAL OF GENERAL CHEMISTRY OF THE USSR IN ENGLISH TRANSLATION

October, 1956

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